# GENETICS

IN RELATION TO

CLINICAL MEDICINE

# GENETICS

## IN RELATION TO

## CLINICAL MEDICINE

BY

F A E CREW

M.D. D.Sc. Ph.D. F.R.S., F.R.C.P.Ed.

PROFESSOR OF PUBLIC HEALTH AND SOCIAL MEDICINE
UNIVERSITY OF EDINBURGH

OLIVER AND BOYD

EDINBURGH: TWEEDDALE COURT

LONDON 98 GREAT RUSSELL STREET W.C.

1947

TO

JOHN FRASER ROBERTS

FROM WHOM I HAVE RECEIVED
FAR MORE THAN I EVER GAVE,
A TOKEN OF MY AFFECTION AND
GRATITUDE

# PREFACE

I HAVE been required to offer courses of instruction in Genetics to medical students since the year 1919. For their assistance I fashioned my lecture notes into a book called *Organic Inheritance in Man* which was published just twenty years ago This very rapidly lost its usefulness as the subject of human genetics grew and as my ideas concerning the methods of teaching changed. By 1938 I had decided to bring out a revised edition of the book, but immersion in the affairs of the 1939 International Genetical Congress and engulfment in the war prevented my doing so until now This book, like its predecessor is not meant to be anything more than an edited compilation of lecture notes It is offered as an aid to those who have listened rather than to those who have to learn their genetics solely by reading For the latter there are far better books than this. Of those published in this country the best is J A. Fraser Roberts *An Introduction to Medical Genetics* E. B Ford's *Genetics for Medical Students* is another useful one. The only excuse for producing yet another which cannot possibly be better than these and which indeed cannot be very different in respect of content is that it seems desirable in my view that the many students who in each year must listen to me whilst I strive to attract their eager interest to a subject which has given me such unbounded pleasure, should be able to check that which I said against that which I have written. I lose my enjoyment and my audience if its members must scribble as I talk. This book is written so that they may not be forced to write If it remains the only genetical text read by students of mine then my teaching will have been most imperfect, as imperfect as will be the knowledge of clinical genetics possessed by those whom I have taught.

To provide such an introduction to genetics is by no means an easy task for anyone who has personal knowledge of the medical student and of the strenuous and heavily loaded courses into which he is plunged The student quickly learns that the quality of a subject is to be assessed according to its relative

importance in his examinations and to its promised usefulness in the job of earning a living or of gaining promotion within his chosen profession One that is merely intellectually stimulating or satisfying cannot be allowed to claim his rapt attention. Interest must be harnessed to utility The student is forced by circumstances accepted by his teachers and created by the most clamant needs of society to seek, above all else, the power to treat and cure even though this be gained without an understanding of what he does.

So it is that the geneticist, eager to share with others the joy of discovery and to display the considerable attractions and possible usefulness of his subject, encounters embarrassment at the start. It has to be admitted that the gifts he proffers cannot compare in respect of immediate usefulness with those that bedeck the laboratories of the biochemist or the radiologist, for example It is not to be expected that, to one whose conditioned ambition it is to treat the sick or injured human individual genetics can exercise a strong appeal

Faintly remembering the remote days when he was reluctantly introduced to the intimacies of the slimy frog and the stinking skate, and still wondering what on earth these things had to do with matters medical, the student is in no mood to appreciate the attractions of the special genetics of the fruit fly or of the mouse. To call upon the vast store of genetical knowledge that has been accumulated through the intensive study of forms other than man, knowledge well worthy of serious consideration by those who are concerned with programmes of human and social amelioration, is a sure method of persuading the average student that the science has little or no value to himself He is not interested, he cannot afford to be interested in comparative genetics in the latter part of his curriculum. He is concerned with the acquisition of that limited corpus of knowledge and of that small constellation of skills that will enable him to find a place in clinical medicine with its dramatic episodes its human contacts and its emotion-satisfying rewards. He is interested in the individual not in the species in the present and not in the future.

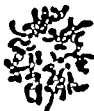
So that if genetics is to be made attractive it must be offered as the special genetics of man, a difficult task in itself since knowledge in this field is so incomplete It must deal with individuals and very small groups such as the family

and not with large populations. If the student can be persuaded that the children yet unconceived are as much the patients of the physician as are the moribund senescents on whom he is preparing to lavish his care that the population needs medical attention no less than do the individuals who in their combination comprise it that the practice of medicine is much more than a means of achieving self-satisfaction, social security and elevation that it is in fact among the most potent instruments which mankind is using deliberately for purposes of human and social betterment, then and only then can the teacher hope to reap satisfaction from his sowing

To the clinician, concerned with the treatment of individual patients genetics has but little to offer that can augment skill or reputation, but to the diagnostician and especially to the doctor who in large or small measure is wishful to play a part in the grand adventure of furthering the best interests of mankind as a whole it has much. It must be the purpose of this book briefly to illustrate genetical fact, to interpret this in terms of current theory and to invite the student to dream of a world in which medicine, as a form of experimental and applied biology is eagerly used in the service of our species

F. A. E. C.

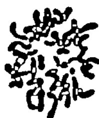
ABCOTA 1946



# CONTENTS

CHAPTER VI





# CHAPTER I

## Is a Knowledge of Genetics really necessary?

It is now generally accepted it would seem, by those who are responsible for the construction of medical curricula that the science of genetics has much of value to offer and that therefore an introduction to genetical fact and to current genetical theory should be included at some point. It is recommended for example, that instruction in elementary genetics should be offered during the pre-registration or the pre-clinical years and that the bearing of genetical knowledge upon problems of health and disease should be considered at some length in the courses that lead to such diplomas as those of public health and psychiatry

It is the case that the theory of the gene claims the place in biological thought that years ago was occupied by evolution theory The latter was demonstrably of the very greatest importance to the proper understanding of the role of medicine *as an instrument of social policy Concerning it there is* today no disputation. It is part of the birthright of every individual. There is no longer any need in a University course of medical zoology to offer evidence intended to show that Darwin was probably right. It is enough to base the whole of one's teaching upon the fundamental truths of the theory which is an article of one's faith and an ingredient of one's hope and aspiration.

The theory of the gene is equally invigorating as a theory It is equally important in relation to medicine especially to those aspects of medicine that are concerned directly or indirectly with the cell. But it so happens that its methods are essentially experimental and that many of its techniques of analysis and synthesis which have been employed with such outstanding success in programmes of animal and plant improvement, are directly applicable to both clinical and population medicine. Examples are such as are concerned with the recognition of what is inborn and what is acquired with the mode of inheritance of the abnormal and undesired those which attempt to estimate the expected incidence of

abnormality in a given population or those that relate to the control of such frequency

But there is no need for the geneticist to hawk his wares. It is sufficient for anyone who wishes to convince himself that there is a place for genetics in medical education to consult a standard textbook of medicine The dimensions of this place will be indicated by the frequency with which such genetical terms as familial heredity hereditary genetic or inborn are mentioned in the accounts of ætiology

A rapid search in such a textbook much used by student and practitioner alike revealed that one or other of these terms was included in the discussion concerning the ætiology of certainly not less than fifty-six different diseases This is a small number a mere fraction of the list presented in the *Nomenclature of Diseases* Moreover the great majority of the diseases quoted are relatively rare The genetic element in disease causation should therefore not be given too great a prominence The diseases clearly of genetic origin are not among those which are responsible for the greatest amount of general morbidity and mortality in our population. This is not so in certain special fields of medicine, however For example authoritative opinion presents the view that not less than 10-25 per cent of all deafness is genetic in origin, whilst genetic causes of partial and total blindness account for about 10 per cent. of the whole. Here are some illustrative examples

| | |
|---|---|
| Acholuric jaundice | The disease may be hereditary |
| Hepatomegalia glycogenia | The relatively high incidence of cousin marriages among the parents of affected patients suggests that the condition may possibly be inherited as Mendelian recessive character |
| Cirrhosis of the liver | Is in very rare instances familial, presumably as result of an inborn defect of the liver cells. |
| Pernicious anæmia | There is hereditary proclivity |
| Sickle-celled anæmia | It is hereditary and familial, behaving as Mendelian dominant. |
| Hæmophilia | I Mendelian terminology it is a sex linked recessive. |
| Hereditary Purpura Hæmorrhagica | It is a hereditary disease. It is transmitted directly from generation to generation and affects females twice as often as males (hence the term female hæmophilia ") |

| | |
|---|---|
| Hereditary Haemorrhagica Telangiectasia | Behaving as Mendelian dominant. |
| Gaucher' disease (Splenic and hepatic enlargement) | It is possible that the condition is due to an inborn error of metabolism. |
| Fatty degeneration of the Heart | Heredity is factor |
| Angina pectoris | Heredity is factor |
| Congenital heart disease | Heredity is probably factor |
| Angioneurotic oedema. | Heredity is an important factor |
| Acute bronchitis | It is probable that some degree of hereditary predisposition occurs since weakness of the chest is common in some families. |
| Asthma | Certainly runs in families The heredity is not always direct, the nervous instability sometimes being evidenced in other generations by migraine, epilepsy hysteria. It is believed that an unduly irritable bronchial centre is the facto transmitted by heredity |
| *Pulmonary tuberculosis* | *Children may inherit the tuberculous* diathesis. |
| Rheumatoid arthritis | It does not ppear that the disease is hereditary but it seems likely that there is an inherited diathesis. |
| Osteogenesis imperfecta | The condition is hereditary in 27 per cent. of cases. |
| Osteopsathyrosis | A history of inheritance from generation to generation is common |
| Achondroplasia | The disease may be transmitted through the male line. Its occurrence in three genera tions has been recorded. |
| Eczema | There is possibility of an inherited susceptibility or diathesis. |
| Hydrocephalus | Hereditary infl ences are of importance in the causation of congenital hydrocephalus. |
| Amaurotic idiocy | Nothing is known of the aetiology of the disease apart from its familial and racial incidence. |
| Friedreich ataxy | Indirect heredity is the most common for the reason that the subjects of this disease are usually affected in childhood and incapacitated by the time adult lif is reached so that they do not procreate. Direct heredity is, however by no means as uncommon as has been supposed and in one family the disease has been transmitted from father to son for seven generations. |
| Familial spastic paralysis | The disease is sometimes hereditary but is more commonly familial. |

| | |
|---|---|
| Huntington's chorea | "Further than heredity no causal factors are known. |
| Peroneal muscular atrophy | Heredity plays an important part in its incidence |
| Myotonia congenita | A very rare malady which is hereditary and familial" |
| Dystrophia myotonica | The heredity is homologous, that is, it tends to appear in the same childrank in a number of apparently unconnected families at a common distance from one and the same ancestor and often seems to be entirely confined to one childrank. |
| Familial periodic paralysis | Heredity is very marked and the malady has been traced through five generations. Transmission may occur either through the male or through the female and not infrequently a generation is skipped Several members of the same family are usually affected. |
| Pseudohypertrophic paralysis | In certain incidences a family history is obtained, always on the mother's side. Commonly several children are attacked in each generation. |
| Senile dementia | Heredity is held responsible for the wide differences in mental health among elderly people" |
| Affective disorders | Heredity is the most constant single cause. In the major manic depressive cases the genetic factor is weakly dominant. |
| Schizophrenia | Studies of the incidence in twins and in the members of a family demonstrate a hereditary factor in a majority of cases. If one of a monozygotic pair of twins is schizophrenic the other is also in 70 per cent. of cases. The frequency of the illness among various relatives of patients indicates that it is not transmitted as a simple dominant nor indeed as a simple recessive, probably more than one recessive gene is responsible. |
| Obsessional disorders | The hereditary factor is strong A third of the parents of obsessional patients and a fifth of their brothers and sisters have themselves shown pronounced obsessional traits." |

Certain of these statements can have little or no meaning to the student unless he already has a fairly thorough knowledge of the simpler facts and of the more firmly founded hypotheses of genetics and an acquaintance with its terminology

Genetics (Gk. *genesis* descent) is that branch of the science of Biology which is concerned with the study of the nature and causes of the similarities and dissimilarities in characterisation exhibited by individuals and groups related by a common ancestry This book will attempt to deal with certain aspects of the special genetics of man and in particular with the causes and mode of inheritance of certain characters regarded as pathological and distinguishing the abnormal from the normal the sick from the hale

## VARIATION

The clinician dealing with an individual patient is first concerned with diagnosis—the recognition of the signs and symptoms which in their combination indicate the nature of the disorder from which the patient is suffering Then he seeks the cause of this disorder The value of genetics in clinical medicine lies in the fact that it is concerned with problems of causation, with the causes of the similarities and dissimilarities in the characterisation of related individuals Since the precision and potency of therapeusis must necessarily be affected by the validity of the physician s concept of causation genetics must perforce be of interest and of value to him.

In general it can be said that the causal agents of defect, derangement, disorder disease are of two kinds those that pertain to the individual and those that derive from the environment in which the individual has his being Individuals and environments differ widely among themselves, among them there is much *variation* Genetics though necessarily interested in environmental variations is especially concerned with inborn variations exhibited by living organisms.

The raw material that claims the interest of the geneticist is to be encountered in great abundance in any human congregation. All the component individuals present many *characters* (details of structure or of function) in common all are mammals all are human. Between them there is much fundamental similarity Yet no two are exactly alike. Everywhere there is much dissimilarity much variation.

A railway compartment or a classroom can include repre sentatives of several of the geographical varieties (races) of mankind differing one from the other in respect of skin colour hair texture and so on. There can be a polydactylous individual

an albino a diabetic, a Frenchman a conservative, a Wesleyan methodist. It is a matter of common observation that certain of these dissimilarities e g differences in language, religion, political preferences cultural tastes manners are *acquisitions* pertaining to the *social inheritance* which one generation receives from its predecessors. The changing of babies in their cradles would change all these. But it is equally a matter of common observation that other dissimilarities are not acquisitions are not derived from the physical or social environment of the individual but are innate inborn The offspring of a Chinese couple will be Chinese physiognomically whether born in Canton or Crieff If his parents are negroes the child will be a negro physiognomically whether raised in Gambia or the Gorbals. Certain characters exhibited by the parents and the parental stock are manifestly transmitted to their children and remain largely if not wholly unaffected by differences in experience It is recorded that a family named Little, now living in New Brunswick, is remarkable in that many of its members have a white lock of hair This has been the case for six successive generations The family is related to the Percys. The story is told that after Harry Hotspur was slain at Shrewsbury in 1403 his wife gave birth to a son bearing this white lock. It is no longer credited that emotional distress can be the cause of such morphological abnormality The really interesting fact is that this character white forelock, suddenly appeared in a pedigree and there after has reappeared generation after generation, living at different times in different places and enduring markedly different experiences.

A child when born exhibits a peculiar abnormality poly dactyly for example. Its mother and a sister are normal in respect of digit number but its father and another sister are both polydactylous. It becomes difficult to avoid the notion that these individuals of different generations of the same family are exhibiting the very same abnormality for the reason that, being related they harbour in themselves the selfsame cause of the condition a cause that is constitutional and passes from one generation to the next across the bridge of reproduction. The affected must differ from the normals for the reason that in the latter the cause is absent. When exposed in the same circumstances to the same disease

provoking agency—nutritional deficiency bacterial invasion, occupational hazard—some individuals of a group but not all, succumb Can it not be that constitutional differences must distinguish those who become diseased and those who do not?

It would seem to be reasonable to approach this matter of causation by postulating that differences between individuals of the same group are indeed of two kinds (*a*) *modifications* acquired characters the results of the reactions of the living organism to the impress of environmental forces, to differences in experience, in social tradition, education, occupation climate, socio-economic circumstances and the like, and (*b*) inborn, innate hereditary *genetic characters* which are the expression of precise developmental impulses or tendencies which were present in the individual from its very beginning

If there be such inborn tendencies or inclinations then it is reasonable to look for their material basis If there be such a basis then it must be present within the fertilised ovum in which the individual (the *zygote*) has its origin. If a genetic character is to be inherited from, transmitted by the preceding generation to its successor and if both parents share in this transmission, then its material precursor must be sought for in both spermatozoon and ovum (the *gametes*) which in their union give rise to the zygote itself

It is to be understood that in concentrating his attention upon the constitutional—genetic—causes of variation the geneticist does not assume that the genetic cause operates in a *vacuum*. The end result of the development of the individual must surely be the expression of innate tendencies inborn capacities reacting to the general environment or else to specific ingredients of this. An inborn capacity to become a tall individual, for example must remain a potentiality so long as malnutrition faulty hygiene or frequent illness deny the individual the opportunity for its expression. Nature and Nurture are the forces which, in their interplay fashion the characterisation of the individual But quite commonly it is necessary to disregard much and to concentrate upon a little in order to advance knowledge. In order to recognise the role that Nature plays in the fashioning of a characterisation it is necessary to disregard Nurture as far as is reasonably possible This is done by considering genetic variations as they occur in an environment that has been made as uniform and constant

as possible. Alternatively genetic similarity can be studied as it is expressed in a variety of environments. In these ways the roles of Nature and Nurture can be disentangled and the relative importance of the two can be assessed.

A survey of the hereditary differences which distinguish related individuals suggests that whilst certain characters, e.g eye colour the blood groups are in their development seemingly quite independent of the environment, being the direct expression of initial and inborn differences others life expectancy for example, are expressions of hereditary tendencies more or less affected by environmental forces

## The Search for the Cause of Genetic Variation

It is established that the sole physical link between the generations consists of the two gametes Together they form the only bridge across which the physical basis of organic *inheritance can pass from one generation to the next. It is* established further that fertilisation and conception consist not so much in the union of male and female gametes as in the fusion of their nuclei.

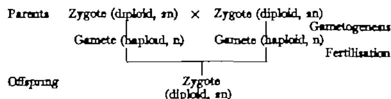
The nucleus is built up of a variety of protoplasm called ***chromatin*** which is remarkable for its appetite for such basic dyestuffs as hæmatoxylin and gentian violet and which exists in the form of a number of discrete lumps or rods known as ***chromosomes*** (Gk. ***chroma*** = colour ***soma*** = body) The number of chromosomes present in the nuclei of the cells of a given animal or plant is characteristic for that particular species The number in ***homo sapiens*** is 48

Owing to the fact that these chromosomes are heteromorphic, differing among themselves in respect of size shape and behaviour during cell division it has been demonstrated that these 48 chromosomes are present in the form of 24 pairs. With one major exception to be considered later the two members of a given pair are identical in respect of size, shape and behaviour For this reason they are known as ***homologous chromosomes***

If the number of chromosomes is to remain constant and characteristic for the species and if the ripe gamete carries chromosomes in its nucleus as do all the nuclei of all the somatic cells it would seem that the number of chromosomes in the mature gamete must be half that in the fertilised ovum and

in the cells which derive therefrom. Cytology that branch of biology which is especially concerned with the study of the anatomy and physiology of the cell has shown that this is so and that this half (*haploid*) number (n) is built up of one member of each pair of chromosomes present in the somatic nuclei. The number typical for the species is therefore a double set of chromosomes. This *diploid* number (2n) is established at the moment of fertilisation by the union of two haploid sets one of which was received by the zygote by way of the spermatozoon from the father the other by way of the ovum from the mother

The delicate precision of this mechanism is such that it would seem to furnish the means whereby the physical pre cursors of genetic characters if there be such, could be distributed from parents to offspring in an orderly fashion. There is no structural unit other than the chromosomes themselves which behave in a way which ensures that they are reduced to one half their number in *gametogenesis* (the formation of the gametes *oogenesis* and *spermatogenesis*) and are restored to their constant and characteristic diploid number as the result of fertilisation




Since it is intended to present the argument that the chromosomes are in fact the vehicles of minute structural units the hereditary factors, the *genes* which are the causes of genetic resemblances and dissimilarities among related individuals, it is necessary to pay attention to their behaviour in *mitosis* and *meiosis* (*mitos* = a thread *meion* = smaller)

In a cell (with the diploid number of chromosomes) about to divide the nucleus undergoes mitosis a process which for purposes of description is conveniently divided into five stages —prophase, prometaphase, metaphase, anaphase and telophase. It is when mitosis is completed that the cell itself becomes increasingly constricted about its middle and breaks across at this constriction to form two new cells

PROPHASE. *The chromatids and the spindle attachment are revealed.* The chromosomes lose water to become denser. They are now in a condition in which they can be fixed, stained and thereby mad easily visible. It is seen that each chromosome has formed a replica of itself. The original chromosome and its replica are now known as *chromatids*. The number of these bodies is therefore the *tetraploid* (4n). Every chromosome possesses a short region, the spindle attachment, which does not stain. In this region the two chromatids remain united throughout prophase. The position of the spindle attachment in the length of the chromosome is constant for any given chromosome but varies from chromosome to chromosome.

PROMETAPHASE. *The centrosomes and the spindle take up their position.* There is a double granule, the *centrosome* which lies outside the nuclear membrane. *At the end of the prophase its two parts separate and move* to opposite ides of the nucleus, remaining connected by modified region of the cytoplasm known as the *spindle*. At the onset of prometaphase the nuclear membrane disappears and the axis of the spindle comes to lie along a line joining the two centrosomes. Each chromatid organises the nuclear sap into additional spindle elements.

METAPHASE. *The coiling f the chromatids.* These lie in the form of a flat plate on the equator of a system the poles of which are the centrosomes and are attached to the spindle at their spindle attachments, their long arms stretching out into the cytoplasm. The two chromatids derived from each chromosome now lie so close together that the division between them is scarcely discernible. They have assumed the form of a tightly coiled spring within a thin pellicle.

ANAPHASE. *The splitting of the spindle attachments and the separation of the chromatids.* Each spindle attachment splits into two parts and these repel one another. Thus the two chromatids are dragged apart in opposite directions towards the poles of the spindle. The chromatids of prophase now become the daughter chromosomes of anaphase.

TELOPHASE. *The final stages of the formation f two daughter nuclei.* The separated sets of daughter chromosomes come to rest and undergo a series of changes, the reverse of those which happened in prophase. A nuclear membrane forms around each of th two new nuclei, the chromosomes imbibe water to swell and to become increasingly difficult to fix and stain.

Mitosis is the device by means of which each and every cell having its origin in the fertilised ovum shall become possessed of an exact replica of the chromosome content of this original cell.

Meiosis is a modification of mitosis and is peculiar to gametogenesis. Essentially it consists of two divisions of the nucleus (first and second meiotic divisions) with but one division of the chromosomes. The *first meiotic division* is divisible, as is an ordinary mitotic division into prophase, prometaphase metaphase, anaphase and telophase, but its prophase is further divided into four stages, the leptotene, zygotene, pachytene and diplotene.

LEPTOTENE. The chromosomes appear as fine coiled threads not yet split into chromatids (the time of the formation of the chromatids differs significantly from that in mitosis). A series of darkly-staining granules, the *chromomeres* can be detected along the lengths of the chromosomes. The relative positions of these chromomeres is constant for a given chromosome.

ZYGOTENE. The homologous chromosomes come together pair as the result of an attraction between identical chromomeres. As the result of this pairing of homologous chromosomes haploid number ( ) of *bivalents* (double chromosomes) is formed. That they do consist of double chromosomes is proven by the fact that each bivalent has two spindle attachments.

PACHYTENE. The members of each bivalent wind themselves around each other Then the chromosomes split into chromatids to form *tetrads*. Each bivalent consisted of two chromosomes now each of these chromosomes has given rise to two chromatids so that there are four bodies, tetrad, in the place of the original pair of chromosomes.

DIPLOTENE. Between the two chromatids derived from the different members of the chromosome pair *chiasmata* appear A chiasma is a cross and represents sticking a breaking and reunion with interchange of material of the chromatids concerned. This interchange is known as crossing-over and it is this that gives the appearance of an X. As many as eight chiasmata are not uncommon. They do not occur very near together because the chromatids are stiff enough to resist close twisting The occurrence of one chiasma therefore prevents the formation of another nearby

After the chiasmata have formed, the chromatids shorten, thicken and rotate.

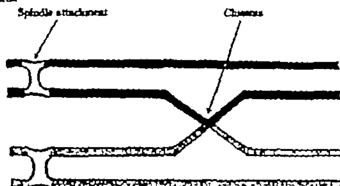



FIG. —Diagram of Chiasma formation
Solid black = paternal chromosome, split into chromatids
Stippled = maternal chromosome, split into chromatids

Breakage and reunion occur after the chromosomes have split but before they have separated. Breakage and reunion therefore precede the appearance of the chiasma, in fact they give rise to the chiasma. Note that paternal chromatid is associated with paternal chromatid—and maternal with maternal—on either side of the chiasma. A chiasma is visible sign that genetical crossing-over has occurred.

PROMETAPHASE and METAPHASE are as in mitosis.

ANAPHASE. The spindle attachments do not divide as in mitosis. This failure of the spindle attachments to divide is peculiar to the first meiotic division. When those of homologous chromosomes begin to repel one another they drag apart pairs of chromatids which, consequent upon crossing-over contain sections of both paternal and maternal origin. This, then, is the significant difference between the anaphase of mitosis and of the first meiotic division. In mitosis the diploid number of undivided chromosomes moves from the equator towards each pole. In meiosis it is the haploid number of chromosomes that so moves, but since each of these chromosomes is divided into a pair of chromatids held together at the spindle attachment the number of bodies that moves is the same—the diploid—in both cases.

TELOPHASE is as in mitosis.

The *second meiotic division* differs from mitosis and from the first meiotic division in the following ways. There can be an interphase between the telophase of the first meiotic division and the prophase of the second, or the prometaphase of the second can, without a pause, follow upon the telophase of the first.

PROMETAPHASE. The chromosomes are of the haploid number They are split into chromatids held together by their spindle attachments.

METAPHASE, ANAPHASE and TELOPHASE are as in mitosis save that they result in the production of cells containing the haploid number of chromosomes. No new division of chromosomes occurs and all that happens is that the chromatids left together at the first meiotic division pass to opposite poles of the spindle. As a result of the first and second meiotic divisions four cells—four spermatozoa or an ovum and three abortive polar bodies—are formed, each carrying the haploid number of chromosomes.

For further and fuller information the reader is referred to a book on cytology for example M J D White' *The Chromosomes* (Methuen).

## THE SEX-CHROMOSOMES

Male is to be distinguished from female by reference to the chromosome content of the nuclei of their constituent cells. The two sexes differ in respect of one pair of chromosomes known for this reason as the *sex-chromosomes* The rest of the chromosomes are referred to as *autosomes* In the human female the sex-chromosomes have the form of a pair of identical members One of the sex-chromosome pair of the male is similar to these These three are known as the X-chromosomes The X of the male has an unequal partner called the Y chromosome The (diploid) chromosome constitution of the human female is therefore

| | |
|---|---|
| autosomes | 23 pairs of homologous chromosomes |
| sex-chromosomes | a pair of homologous chromosomes (XX) |

whereas that of the male is

| | |
|---|---|
| autosomes | 23 pairs of homologous chromosomes |
| sex-chromosomes | a pair of unequal chromosomes (XY) |

*The haploid set in every mature ovum consists of 23 autosomes* plus an X but of spermatozoa there are two kinds one with 23 autosomes and an X and one with 23 autosomes and a Y

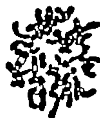
The female is ***homogametic*** elaborating but one kind of ovum in respect of chromosome constitution, whereas the male is ***heterogametic*** producing two kinds of spermatozoa, an X-chromosome-bearing kind and a Y bearing

Any ovum fertilised by an X-bearing spermatozoon will yield an XX zygote, a female. Any ovum fertilised by a Y-bearing spermatozoon will yield an XY zygote, a male. The Y-chromosome is the peculiar property of the male and it passes from father to son. The heterogametic mechanism ensures the production by a mated male and female of both male and female offspring

It is necessary to devote a few lines to an explanation in genetical terms of the actual sex-determining mechanism. In a species in which male and female forms occur maleness and femaleness are in the ultimate analysis genetic characters. In the constitution of every individual, male and female alike, there are a great many genes which are partly or wholly concerned in the control of the sex-dimorphic characters Some are male-determining, others are female-determining Both kinds are scattered throughout the chromosomes auto-somes and sex-chromosomes alike. In a species like our own as the result of chromosome fragmentation and recombination the chromosome complex as we now know it came into being The X-chromosome in its construction came to include a relatively large number of female-determining genes, whilst among the autosomes and in the Y-chromosome a preponderance of male-determining became congregated. The result is that there is a male set and a female set and between them there is a balance. In the female, XX the relationship of the two is that the female set is greater than," stronger than the male In the male, XY the relationship is such that the male set is predominant. Quantitative disturbances of this autosome Y-chromosome and X-chromosome relationship would be expected to lead to disturbances in sexual

characterisation. An XY individual because it is an XY individual develops testes and becomes a functional male. A genetic female XX develops ovaries and therefore becomes a functional female. Abnormality in respect of the endocrine products of the gonads (testis and ovary) would be expected to lead to abnormalities in the final sexual characterisation. But these are matters which belong not to genetics but to developmental physiology. If information concerning them is sought, F. H. A. Marshall's *Physiology of Reproduction* should be consulted.

CONCEPTION. It is whilst the oocyte is undergoing meiosis that it is entered by the mature spermatozoon which promptly loses its tail. As soon as the spermatozoon has entered a membrane forms around the ovum which prevents the entry of any other male gamete. The nucleus of the ovum passes into anaphase of the second meiotic division. The haploid nuclei of ovum and spermatozoon fuse to form the zygote with the diploid chromosome number. This diploid nucleus next divides in the usual mitotic fashion to form the first cleavage cells of the newly formed embryo.



## CHAPTER II

*It matters little to be born in the duckyard when one comes from a swan egg* The Ugly Duckling.—Hans Anderson.

### THE THEORY OF THE GENE

THIS postulates that the inherited characters, physical and mental, normal and abnormal, anatomical physiological and pathological are controlled by genes resident in the chromosomes of the nucleus. The genes are present in pairs and of each pair one member is derived from the father and the other from the mother The gamete contains only one member of each pair of genes present in the constitution of the individual who elaborated these gametes Each gene has its own particular place (*locus*) in the length of a particular chromosome and the genes in any given chromosome are arranged in a linear order Homology in respect of chromosomes now assumes a different meaning Homologous chromosomes are such as accommodate the same series of loci. Genes resident in the same chromosome will remain together *linked* in transmission so long as the chromosome retains its integrity Crossing-over between members of a pair of homologous chromosomes can disrupt such linkage. The number of groups of linked genes—*linkage groups*—is the haploid number of chromosomes that is characteristic for the species.

The genes in their action, presumably chemical in kind, affect the processes of development and degeneration, influencing their timing rate and direction. In so doing they introduce forces which tend to mould the characterisation of the individual For practical purposes it is often convenient to correlate one gene with one character hence the notion of a *unit character* But most, if not all characters are the product of the interaction of several genes. It is possible that very many genes, possibly all the genes in the constitution of the individual—the *genotype*—play a part in the fashioning of any one character Nevertheless it is usual for one gene to be the principal agent in the production of a given character and it is therefore convenient to regard this one as being that which

causes which yields the character If a gene has a discernible effect on several characters it is said to be *pleiotropic* When this is the case the name given to the gene is derived from its most striking effect.

Any gene can undergo *mutation* a spontaneous alteration of its internal organisation which is reflected in a corresponding *alteration in the character which it evokes* Through mutation a new heritable variation comes into being The unmutated gene yields normality the same gene, mutated affects the same developmental processes of the same tissue or organ but yields a different end-result, something different, a variation a deviation from normality a defect. The unmutated and the mutated forms of the same gene are for convenience sake spoken of as *allelomorphs* or *alleles* (different forms or states of the same gene)

Mutation can occur at any time when the gene is producing a copy of itself (the formation of the chromatids) It can take place therefore during ordinary somatic cell division—*somatic mutation*—and it can occur during gametogenesis—*gametic* mutation. Each gene has its own mutation frequency and the rate of spontaneous mutation ranges through a wide variety of animals and plants from about 1 in every 50 000 to around 1 in 120,000 life-cycles The mutation rate can be greatly increased by the use of X-rays and other high-energy radiation ultraviolet light certain chemical substances such as mustard gas and to a lesser degree by sublethal temperatures. In the case of X-rays the increase is proportional to the dosage as measured by ionization but is independent of the wavelength and of the intensity of the radiation There is no threshold of ionization below which no mutations are produced Knowing the spontaneous mutation rate it therefore is possible to calculate the amount of ionization necessary to produce it It has been suggested that cosmic radiation and naturally occurring radioactivity may perhaps produce that amount of ionization which is necessary There is considerable disagreement concerning this matter For the present the cause of spontaneous mutation remains unknown. To a chemist it would not be surprising to find that different internal organisations different spatial arrangement of elements were associated with different mutation frequencies Some would be in virtue of their organisations more stable than others Perhaps this

is the explanation of some of the differences between the rates of spontaneous mutation of different genes Random temperature oscillations within the nucleus may be another possible cause of this mutability

The fact that mutation can and does occur in both directions normal allele to mutant allele and mutant allele back to normal allele shows that mutation does not involve a loss of gene material

Each gene it has been stated has its own particular locus in a particular chromosome. By this is meant that in this particular locus one or other allelomorphic form of a particular gene is to be found. At a particular level, or point in their length, of a pair of homologous chromosomes there is a pair of loci in which the pair of genes for this or that particular character reside. The two loci may be occupied by the same allelomorphic form. The individual is then said to be *homozygous* in respect of the particular allele gene, in question. On the other hand, there can be different alleles in the two loci. The individual is then said to be *heterozygous* (having two dissimilar alleles). The states of homozygosity and heterozygosity result from the facts that two individuals are involved in the production of zygotes, that in the genotypes of these individuals there are many thousands of gene pairs consisting of similar or dissimilar mates and that in respect of many genes these parents can differ one from the other

The mutated gene may be a *dominant* or a *recessive* in relation to the allele from which it arose. If it is a gametic dominant the character based upon it will appear in the next generation If it is a gametic recessive it will remain unsuspected and unexpressed until it happens that two individuals each heterozygous in respect of it, mate and reproduce. Then and only then does it become possible for the homozygous recessive to appear and the individual exhibiting a recessive character must be homozygous in respect of the gene in question Recessive characters therefore are usually displayed several zygotic generations after the mutation has occurred.

In the case of a dominant somatic mutation all tissues which are derived from the cell which first received the mutated gene will possess it and the character based upon the gene will be expressed if these tissues happen to be involved in the formation of the appropriate organ Manifestly a mutant gene affecting

the colour of the eye will have no affect if it is a somatic mutation and has occurred in a cell which, multiplying forms the tissues of the foot. A somatic mutation can yield a mosaic or chimera. *Heterochromia iridis* would seem to be an example of mosaicism with a patch of a dominant character on a recessive background or vice versa. The gonads themselves can be affected by a *somatic mutation* so that the genotypic constitution of their elaborated products—the gametes—can be different from that of the bulk of the soma of the individual that produced them. The parent would be a mosaic, the greater part of his body being built of cells in the nuclei of which there is the unmutated gene whilst in the nuclei of the cells of the rest and of the gonadic tissue there would be the mutated gene.

The genotype is the genetical basis of the characterisation of the individual The *phenotype* of the individual the sum of its characters, is the expression of this genotype this expression being suppressed, encouraged modified by various agencies within the environment of the living individual.

The action of a gene can be affected not only by environmental agencies but by that of other genes in the same genotype. Thus in different individuals with different genotypes the character based upon the gene in question can vary in the mode or degree of its expression.

To demonstrate the reasonableness of all these statements by reference to illustrations of organic inheritance in man is not without difficulty The human subject is by no means a satisfactory experimental material from the point of view of the geneticist. He cannot be kept in a cage or restrained by wire-netting his mate is not to be chosen for him he matures slowly and produces few offspring his chromosomes are numerous and his mutation rate cannot be speeded up deliberately by the use of X-rays. So that for genetical studies of man methods other than those employed in the case of the usual laboratory animal material must be adopted. Studies of pedigrees the comparison of the phenotypes of identical twins, the study of the effect of parental consanguinity upon the incidence of particular characters among the offspring and the application of sophisticated statistical techniques to data produced by the occurrence of unusual and abnormal characters in large populations have all added considerably to our

knowledge, and against the background of general genetics and of the special genetics of other forms enough of human genetics is already known for its value in application to be assessed

It is but natural that our knowledge of the genetics of grossly abnormal conditions should exceed that concerning normality They are more easily described identified and traced Because of their ugliness and of their effects upon viability and functional efficiency they attract attention. But if abnormality is inherited so also is normality if ugliness so also is beauty and the mechanism is the same in both cases

## The Mendelian Laws of Organic Inheritance

At this point it is desirable and necessary to refer briefly to the personality and to the work of Johann Gregor Mendel (1822-84), for if we see far into the nature of organic inheritance it is because we stand on his shoulders Mendel was a member of the Augustinian Monastery of St Thomas at Brno in Moravia. During some eight years he carried out experimental breeding work with the edible pea (*Pisum sativum*) in the monastery garden. In 1865 his famous paper Experiments on Plant Hybrids was published in the proceedings of the local Natural History Society where it lay unnoticed until 1900 when it was brought to the notice of the biological world by three men independently de Vries (Holland), Tschermak (Austria) and Correns (Germany)

Mendel was by no means the first to find himself interested in the problems of hybridisation. He differed from his predecessors in that he did not think of the individual as the unit to be studied but of the various details of structure which in their combination make up the individual. He did not attempt to hybridise representatives of different species but made use of the several varieties of one and the same easily grown cultivated plant. He was able to construct a list of contrasted characters e.g tall stem and short stem, that were to be found in the different varieties and designed experiments whereby he might hope to determine what for example, the stem length character of the hybrid would be when one parent was tall and the other short and thereafter to find out what happened in respect of these characters when these hybrids in their turn produced another generation. Out of this experimentation two " laws emerged.

### Mendel's First Law The Law of Segregation

This states that characters are controlled by pairs of factors, the members of which separate segregate from one another during the formation of the germ cells and pass into different gametes The pairs of factors are restored at fertilisation which allows of their recombination in definite proportions The characters controlled by these factors may also segregate appearing in subsequent generations with definite numerical frequencies.

The first hybrid generation ($F_1$) derived from a cross of true breeding parents is uniform. In the second hybrid generation ($F_2$) segregation of characters occurs in definite numerical proportions.

Mendel's explanation of the results he obtained postulated the existence of corpuscular entities the hereditary factors present in the zygote in pairs but in the gamete only singly In gametogenesis these factor pairs segregated one and only one passing into each gamete To the new zygote each gamete contributed one member of each factorial pair Nothing is simpler or more reasonable than to translate these postulates into the observed facts of cytology If the chromosomes themselves are the factors of Mendel the genes as we now call them, or if they are the vehicles of the genes their behaviour in meiosis fulfils all the requirements of Mendel's first law

### Mendel's Second Law The Law of the Independent Assortment of Characters

If several pairs of contrasted characters enter into the same cross *these segregate independently of each other*

The first law is still undisturbed. It has been shown to be universally valid. This is not so in the case of the second law It still holds good for characters whose genes are resident in different chromosomes As for genes resident in one and the same chromosome *the phenomenon of linkage—the tendency* for genes to be transmitted in blocks—disrupts this independent assortment of characters

The relation of chromosome distribution in mitosis and meiosis to the distribution of inherited characters had not been revealed in Mendel's time He thought not of genes in

chromosomes but of factors in the germ plasm. In the following illustrations of Mendelian inheritance it will be convenient to combine both Mendelian and gene explanations

### *An Autosomal Dominant*

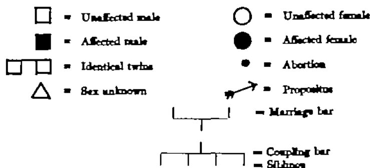
*Ptosis* of the eyelids is the condition in which the upper eyelid cannot be elevated so that the palpabral fissure is much narrowed to give to the individual the appearance of a sleepy and indolent creature having been suddenly surprised. This is a serious hindrance and a most distressing embarrassment. It can result from injury to the eyelid from paralysis of the third nerve or of the branch of this which supplies the *levator palpabræ superioris* or of the sympathetic supplying the smooth muscles of the *musculus tarsalis superior* A weighty tumour can drag down the lid. The *occipito-frontalis* muscle is used to compensate for the loss of the lid-elevating muscles and the forehead is transversely wrinkled In severe cases this procedure fails to uncover the pupil and the eyeball is rolled downwards and the head thrown back to compensate for the deflection of the optical axis. When such causes are operating the ptosis is apt to be unilateral. But there are instances of this condition in which these causes are absent and in which the ptosis is bilateral. These can be cases of hereditary ptosis. For this reason the diagnostician will include among his enquiries the question Does any relative of this individual also suffer from ptosis? The information he collects enables him to construct a pedigree e.g Fig 2

A study of this pedigree shows that the patient ($III_4$) —the *propositus*—has an affected sister and a brother and two sisters who are normal that their mother ($II_4$) was affected and that she married an unrelated normal man ($II_6$) and, furthermore, that she had an affected brother ($II_3$) unmarried and two unaffected brothers twins ($II_5$ and $II_2$) and an unaffected sister ($II_6$), whilst the first pregnancy of her unaffected mother ($I_2$) had resulted in a miscarriage ($II_1$). The grandfather of the propositus ($I_1$) had been affected. The marriage of an unaffected uncle of the propositus ($II_2$) with an unaffected woman ($II_3$) had yielded a group of three *siblings* (brothers and sisters) all unaffected So that the condition had been exhibited by some but not by all the related individuals of three successive generations and both males and females

were affected. Every affected individual had had an affected parent. The offspring of affected × normal included affecteds and normals and normals related to affecteds had produced when mated with normals none but normals.

PTOSIS

Fig. 1.—Pedigree of Ptosis, an autosomal dominant




I, II III etc. = The successive generations
1 2, 3, 4, etc. = Individuals comprising generation
Siblings in order of birth, oldest on the left

These are the characteristic features of completely *dominant* Mendelian inheritance The genetic interpretation of this mode of inheritance is as follows. Hereditary ptosis is a genetic character It is caused by it is the expression of the action of a gene the gene for ptosis. This gene is an allele of a

normal gene which, in its action upon the processes of development yields normality an absence of abnormality It arose from this normal gene through mutation. In an individual heterozygous for this mutant gene, having this in one member of a particular pair of homologous chromosomes and its normal allele in the same locus in the other the two compete for the mastery Which of them shall control the processes of development? That which is the stronger (?) that which comes into action before the other (?). Should one exert its action to the total exclusion of the action of the other the one that prevails is said to be dominant, the one that is suppressed the recessive member of the pair For convenience sake the characters themselves ptosis and normality are spoken of as being the dominant and recessive members of a pair of contrasted characters But in reality t is the gene and not the character that is dominant or recessive.

It has come to be usual to distinguish between two alleles one dominant one recessive, one mutant the other the unmutated form, in one of several ways. The capital initial letter of the name given to the dominant character is often used to designate the dominant gene which in its action has produced it, the corresponding small letter to indicate the recessive allele. P = the mutant dominant gene for ptosis, p = the recessive allele for normality or the symbol + or to be more precise +P can be used for the unmutated gene and P for the mutant dominant allele. It matters little what system is used though it is obviously desirable that as much uniformity as possible should be observed What is important is that the writer and the reader should see a chromosome and a locus and a gene whenever a symbol for that gene is encountered. The transmission of genetic characters from generation to generation as depicted in a pedigree will have but little meaning until in the mind's eye the chromosomes are seen dancing and manoeuvring pairing and parting being torn and tossed during meiosis and mitosis. To the geneticist the character is but the glow of a tracer indicating the movement of the gene itself.

An individual with hereditary ptosis may be a homozygote. This is unlikely since it is most exceptional for both of the parents of the individual to have exhibited the condition. However assume that the individual (male or female) is

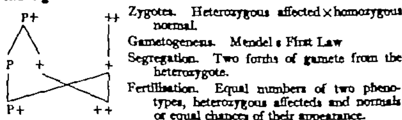
homozygous. Then the genetic constitution in respect of this gene would be PP The following matings are possible —

PP×++ homozygous affected×normal,
PP×P+ homozygous affected×heterozygous affected,
PP×PP homozygous affected×homozygous affected.

Or the individual with hereditary ptosis may be a heterozygote P+ when the following matings are possible —

P+×++ heterozygous affected×normal,
P+×P+ heterozygous affected×heterozygous affected,
P+×PP heterozygous affected×homozygous affected.

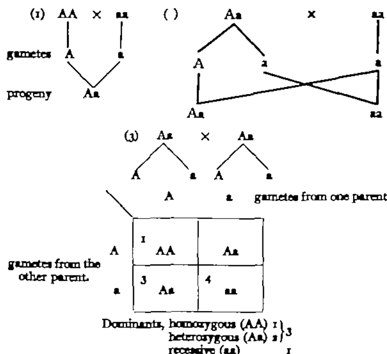
Any of these matings can furnish the parental generation (the *first parental generation* or $P_1$, in order to distinguish this from a grandparental generation, $P_2$, and so on) in a breeding experiment. The offspring produced by such a $P_1$ form the $F_1$—the *first filial generation*—those produced by inter-mated individuals of the $F_1$ produce the $F_2$ and so on. Since neither brothers and sisters nor parents and offspring intermarry in our society the sequence $P_1$, $F_1$ $F_2$ or the back cross the mating of an $F_1$ individual with one or other of the $P_1$ individuals will never appear in a pedigree (save when incest is involved) The modified use of these symbols in human genetics is convenient, however Consider the mating




Using the same system the results of all the other possible matings involving the P gene can be predicted It will be best however to make use of a pair of purely hypothetical genes A for a dominant character and a for the corresponding recessive in order to show that the scheme has a universal application and does not refer solely to ptosis. AA = homozygous dominant, Aa = heterozygous dominant, aa = recessive.

*Observed Facts* AA × AA = 100 per cent. AA
aa × aa = oo per cent. aa
AA × aa = 100 per cent. Aa
AA × Aa = 50 per cent. AA, 50 per cent. Aa
Aa × aa = 50 per cent. Aa, 50 per cent. aa
Aa × Aa = 5 per cent. AA, 50 per cent. Aa, 25 per cent. aa.

The explanation of these facts can be displayed in the following way —




Dominants, homozygous (AA) 1 } 3
heterozygous (Aa) 2 }
recessive (aa) 1

It will be noted that mating (1) is the $P_1$ of a typical Mendelian monohybrid experiment, an experiment in which the parents differ one from the other in that one is homozygous in respect of the dominant member of a pair of alleles whilst the other is homozygous in respect of the recessive member This mating produces an $F_1$ which, since dominance is complete, is remarkable for the uniformity of its phenotype. This uniformity rests on the fact that all the individuals have the very same genotype (Aa) and have not come to differ among

themselves through the action of any other genes in their respective genotypes or as the result of differences in experience.

Mating (2) is the typical Mendelian back-cross the mating of a heterozygote with the recessive parental form. It will be noted that segregation is more likely to be recognised among the progeny of a back-cross than among the $F_2$ produced by the mating of two $F_1$ individuals (see mating 3). The chances of a recessive appearing in an $F_2$ are 1 in 4 in the progeny of a back-cross they are 1 in 2

Mating (3) is in Mendelian terms, the mating of two $F_1$ individuals to produce an $F_2$ consisting ideally of the different phenotypes and genotypes in the proportions 1 AA, 2 Aa 1 aa. Consequent upon the segregation of the genes (one member of each pair into each gamete) there is segregation of the corresponding characters. The 3 1 ratio of dominants and recessive in the $F_2$ is due to the fact that the dominant gene, whether in the single dose or in the double yields the dominant character

The following points will be noted —

Number of types of gametes in the gametic series produced by each of the parents = 2

Number of possible combinations of these gametes = 4 (4 compartments in the checker board, therefore)

Number of different phenotypes among the progeny = 2 (1 displaying the dominant, 1 displaying the recessive character)

Number of different genotypes among the progeny = 3 (AA, Aa, aa)

It will have been noted that the association within the genotype of a heterozygote of dominant and recessive alleles leads according to the theory to no kind of mutual contamination The alleles leave the heterozygote just as pure as they entered. There is blending of characters as will be shown but this is due, not to gene impurity consequent upon association in a genotype, but to the incompleteness of dominance.

It is seen that in a case of this kind in which there are dominance and recessiveness and in which dominance is complete the individual exhibiting the recessive character must be homozygous for the recessive allele A phenotypically " normal individual cannot be heterozygous for the gene for

ptoms cannot be a carrier of this gene An unaffected individual in a pedigree of a dominant abnormal character is in fact normal. On the other hand an individual exhibiting a dominant character must carry the gene for it but may be homo- or heterozygous in respect of this gene.

It will be shown later that dominance is not an essential feature of the Mendelian scheme. When complete however it is a most useful phenomenon for the reason that the track of the gene can be easily followed by the distribution of the character Within a given pedigree a dominant abnormality can be traced with the same ease in the vertical direction as in the horizontal that is to say the parents or children of an affected individual have the same chance of being affected as have the sibs. If a dominant gene is widespread among the population an appreciable number of AA, homozygous dominants, will be available for mating AA×aa, AA×Aa AA×AA. But if a dominant gene is rare in a population then it is mainly to be found in the heterozygous state. Most sufferers will be Aa and not AA. Matings of rare dominants are therefore almost invariably of the Aa×aa type, heterozygous affected×normal. This is so in the case of the majority of the grossly pathological characters. In most instances it is not known therefore whether in fact two doses of the gene would yield a greater degree of deviation from the normal than does one dose, and in human genetics the term dominant is used to signify nothing more than that the gene in question manifests itself in the heterozygous condition

### *An Autosomal Recessive*

Mutation can yield an allele that is recessive to the unmutated or previously existing gene from which it sprang *Alkaptonuria* is a condition in which, owing to the absence of a particular enzyme, the affected individual excretes in the urine homogentisic acid a derivative of aromatic aminoacids such as tyrosin and phenylalanine. Homogentisic acid gives a dark brown colour to the urine, tends to produce arthritis and a blackening of the bones and cartilages. Alkaptonuria is a recessive character the expression of a gene that is recessive to the normal allele. It follows that the individual exhibiting this character must be homozygous (aa), which means that this gene must have been received by the propositus from both

of the parents who could have been aa or +a in genotypic constitution, either exhibiting the character or else carrying the gene in the heterozygous state its action being suppressed by that of the dominant normal allele.

Since the most usual mating will be that between two phenotypically normal but genetically heterozygous people since most marriages yield but few offspring and since the chances that a child with alkaptonuria will appear are only 1 in 4 it is not surprising that a recessive character such as this should skip a generation, should in fact commonly provide no suggestion that it is inherited at all Only rarely can one secure sufficient information out of which to construct a pedigree that includes three successive generations and so it is that an affected individual can have none but unaffected relatives (either homo- or heterozygous for the normal allele) No technique has yet been evolved for the identification of the carrier of this recessive gene (a) so that ++ and +a individuals are phenotypically indistinguishable. Consider the following pedigree —

ALKAPTONURIA

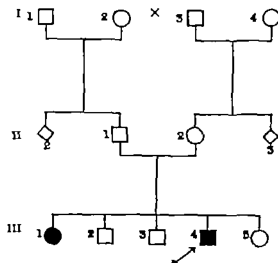



Fig. 3—Pedigree of Alkaptonuria, an autosomal recessive

◇ = Unaffected siblings to the number stated and of no interest in so far as the pedigree is concerned
2

The propositus ($III_4$) is discovered to have one affected elder sister ($III_1$) and two brothers and a sister unaffected. Both parents and their sibs and all four grandparents are phenotypically normal. It is quite impossible from this single pedigree to reach any conclusion concerning the possible genetic basis of alkaptonuria. The affected brother and sister ($III_1$ and $III_4$) could be suffering from the same condition not because they had shared a common parentage, but because they had been exposed to the action of the same non-genetic environmental disease provoking factor. One feature of this pedigree should be noticed, however. The distribution of the condition is horizontal. It is characteristic of a recessive character to show preferential horizontal distribution. The chance of being affected is much higher for the sibs of an affected individual than it is for the parents or for the offspring of this individual. That this is so is due to the prevalence of the Aa×Aa mating since the aa genotype is an extraction from an ancestry in which the Aa is to be found and the Aa genotype yields phenotypical normality.

The diagnostician when confronted with a recessive gene of this kind must perforce turn to the literature, in which information has been distilled from pooled pedigrees involving the same gene. But even this can be unsatisfactory since usually only pedigrees including several affected individuals are recorded. Yet there must be many another full of heterozygotes and with but one or no affected individual. These are not recorded and so false impressions are readily gained. He will learn that a recessive gene can be handed down through many generations unsuspected and unexpressed and that only when by chance two individuals each heterozygous in respect of it, mate and reproduce is the necessarily homozygous exhibitor of the character likely to appear. The vast majority of affected individuals are the offspring of parents who are phenotypically normal but who are in fact heterozygous. There is a *familial* incidence more than one individual i a sibship being affected and the exhibition of the character is significantly more common among the offspring of consanguinous marriages. The phenotypically normal sibs or children of an affected person can be heterozygotes. Finally the offspring of affected×homozygous normal are invariably phenotypically normal those of affected×

affected invariably affected. Here is a pedigree which includes a consanguinous marriage —

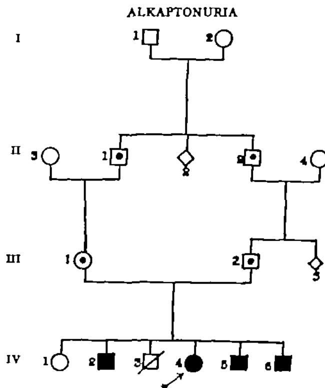



FIG. 4.—Pedigree of Alkaptonuria, showing consanguinity

Here again there is the horizontal distribution and the high incidence among the sibs of the propositus. The parents of the affecteds were the children of two full brothers The chances that both of the parents carry the same recessive gene are increased when they themselves have received part of their genotypes from a common source. Thus if among the parents of individuals exhibiting a particular abnormality there is a higher percentage of consanguinous marriages than in the population at large the possibility that the abnormality is a

genetic recessive is considerably increased. Granting that alkaptonuria in this pedigree is a genetic recessive character then the parents ($III_1$) and ($III_2$) must be heterozygotes The grandparents ($II_1$) and ($II_2$) must also have been heterozygotes There is no reason to suggest that their wives ($II_3$) and ($II_4$) were otherwise than normal. But one of the great-grandparents ($I_1$) or ($I_2$) must have been a carrier of the gene. ($IV_1$) and ($IV_3$) can be either genetically normal or else heterozygous for the gene for alkaptonuria. So

| | | | | | | |
|---|---|---|---|---|---|---|
| I | | | I+a | 2++ | (or 1++ | 2+a) |
| II | | 3++ | I+a | +a | 4++ | |
| III | | | I+a | +a | | |
| IV | I++ or +a | 2aa | 3++ or +a | 4aa | 5aa | 6aa |

Through a long period of time and with the accumulation of many pedigrees it is certain that ultimately records of the following matings and approximations to the following ratios will be obtained to prove beyond all reasonable doubt that a condition such as this is in fact a genetic recessive. In a constellation of varieties of environmental conditions and circumstances the one constant element is the genotype of those who exhibit the condition. A storehouse of pedigrees is an essential requirement in clinical medicine.

| | | | | |
|---|---|---|---|---|
| aa affected | × | aa affected | = | 00 per cent. affected (aa) |
| + unaffected but hetero-zygous. | × | aa affected | = | 50 per cent. unaffected but heterozygous (+a)<br>50 per cent. affected (aa) |
| +a unaffected but hetero-zygous. | × | +a unaffected but hetero-zygous. | = | 75 per cent. unaffected (25 per cent. ++ and 50 per cent. (+ )<br>5 per cent. affected (aa) |

*A Mendelian Dihybrid*

Mendel s second law which states that when two or more factor (gene) pairs segregate simultaneously the distribution of any one of them is independent of the distribution of the others can be illustrated by the use of two other genetic characters, *syndactyly* a condition in which most commonly the third and fourth fingers and toes are webbed or else more or less completely fused, and *albinism*, the condition in which

there is complete or almost complete absence of pigment in the skin hair and eyes The following pedigrees show that syndactyly is a dominant and albinism a recessive character

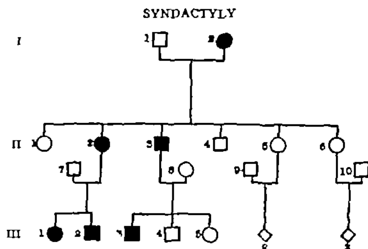



FIG. 5.—Pedigree of Syndactyly an autosomal dominant

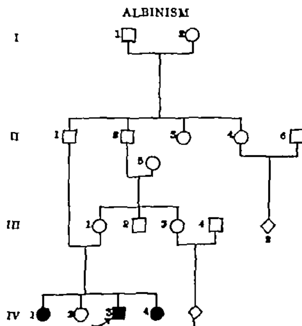



FIG. 6.—Pedigree of Albinism, an autosomal recessive

Suppose that a child exhibiting these two characters comes to the notice of the physician who happens to know that syndactyly has been reported to be a dominant Mendelian character and that albinism is acknowledged to be a recessive Being interested he will at once expect to find that among the sibs of the patient there will be some that are syndactylous that one of the parents exhibits the condition and that in so far as the albinism is concerned it will probably be found that in the pedigree to be constructed a consanguinous marriage will fail to be recorded. He will assume from the start that the patient is most likely to be the result of the mating of two individuals each heterozygous for the gene for albinism and that one of these was heterozygous also for the gene for syndactyly The genotypes of these parents can be represented so —

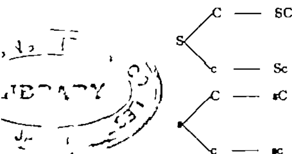
$$\frac{S}{+S} \quad \frac{+c}{c} \quad \times \quad \frac{+S}{+S} \quad \frac{+c}{c}$$

Two pairs of homologous chromosomes are involved—each horizontal line represents such a pair The gene content of the members of the pair is shown above and below this line. It would be confusing to use the sign + to represent both of the normal alleles of the two gene pairs. To the + is therefore added the initial letter of the character a capital S (+S) in the case of the normal allele of the gene for syndactyly since the mutant allele is the dominant member of the pair a small c (+c) for the dominant normal allele of the gene for albinism (= lack of colour). Alternatively the genotypes can be shown as Ss Cc×ss Cc. For the sake of convenience it is proposed to make use of this system, but again it is to be emphasised that the student should so train himself that when he sees a letter he sees a chromosome and when he sees a chromosome he sees a locus with a gene in it.

But for the purpose of making the Mendelian argument as clear as possible it will be best to start with a grandparental generation and to suggest that these grandparents were SS CC and ss cc respectively a homozygous syndactylous individual (who would, in reality probably be non viable) and an albino. It matters not which sex exhibited which character

| | | | |
|---|---|---|---|
| $P_1$ | Homozygous syndactylous normally pigmented | Normal digits albinotic | |
| | SS CC | ss cc | A dihybrid mating involving 2 pairs of genes |
| | SC | sc | Gametes |
| $F_1$ | Ss Cc<br>Syndactylous (heterozygous)<br>Normally pigmented (heterozygous) | | Uniformity of $F_1$, the double heterozygote |

The gametic series produced by such an individual according to the second law of Mendel will be —




The distribution of the S and s pair of chromosomes (genes) is quite uninfluenced by that of the Cc pair. In the production of an $F_2$ two such gametic series will be concerned and these meeting will yield the following genotypes and phenotypes —

| ova \ Spermatozoa | SC | Sc | sC | sc |
|---|---|---|---|---|
| SC | 1 SS CC | 2 SS Cc | 3 Ss CC | 4 Ss Cc |
| Sc | 5 SS Cc | 6 SS cc | 7 Ss Cc | 8 Ss cc |
| sC | 9 Ss CC | 10 Ss Cc | 11 ss CC | 12 ss Cc |
| sc | 13 Ss Cc | 14 Ss cc | 15 ss Cc | 16 ss cc |

Individuals exhibiting the two dominants syndactyly and normal pigmentation —

| | |
|---|---|
| Homozygous for both S and C | Square 1 |
| Homozygous for S heterozygous for C | „ 2, 5 |
| Heterozygous for S homozygous for C | „ 3, 9 |
| Heterozygous for both S and C | „ 4, 7, 10, 13 |
| | 9 |

Individuals exhibiting one dominant and one recessive, syndactyly and albinism —

| | |
|---|---|
| *Homozygous for S* | Square 6 |
| Heterozygous for S | „ 8, 14 |
| | 3 |

Individuals exhibiting the other dominant and the other recessive, normal digits and normal pigmentation —

| | |
|---|---|
| Homozygous for C | Square 11 |
| Heterozygous for C | „ 12, 15 |
| | 3 |

Individuals exhibiting the two recessives normal digits and albinism —

| | |
|---|---|
| Necessarily homozygous for both s and c | Square 16 |
| | 1 |

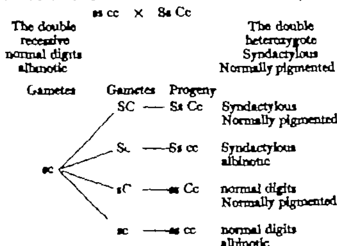
This 9, 3, 3, 1 ratio is the mathematical combination of two 3 : 1 ratios. $(3S+1s)\times(3C+1c) = 9SC, 3Sc, 3sC, 1sc$. It is seen that there is no tendency for the parental combinations of characters to be preserved in the offspring nor for the two dominants and the two recessives to segregate together. The reason for this is, of course, that at meiosis the members of the syndactyly and albino pairs of homologous chromosomes separate one from the other into different gametes at random in the sense that there is no tendency for the paternally or maternally derived elements of each pair to pass into the same gametes together. Consequently the chances that the S or s chromosome becomes included in a gamete with the C or c chromosome are equal. It will be noted that in such an $F_2$ only one individual in every sixteen can be expected to exhibit the two recessive characters in combination.

The trihybrid ratio arising from a mating in which both parents are heterozygous in respect of three pairs of allelomorphs and with dominance leads to a combination of three 3 : 1 ratios independently yielding a ratio of 27 : 9, 9, 9 : 3 : 3 : 3 : 1 $(3A+1a)\times(3B+1b)\times(3C+1c)$. Other ratios have been obtained by computation and by experimentation.

| Number of gene pairs | Number of kinds of gametes produced by F | Number of possible combinations of gametes forming F | Number of homozygous types in F | Number of heterozygous types in F | Number of different genotypes in F |
|---|---|---|---|---|---|
| 1 | | 4 | 2 | 1 | |
| 2 | 4 | 6 | 4 | 5 | 9 |
| 3 | 8 | 64 | 8 | 9 | 27 |
| 4 | 6 | 56 | 6 | 65 | 8 |
| n | $2^n$ | $4^n$ | $2^n$ | $3^n—2^n$ | $3^n$ |

But these are matters which, although of great interest and practical importance to the geneticist and to the creator of new varieties of animals and plants cannot claim a value in clinical medicine.

Mendel's second law can more easily be illustrated by the use of a back-cross of an Ss Cc individual to a double recessive, so —




This mating yields equal numbers (*or equal chances*) of the two dominants : one dominant, one recessive : the other dominant, the other recessive : and the two recessives. The mating that was suggested as the most probable origin of the

syndactylous albinotic child was Ss Cc×ss Cc. This would yield —

Ss Cc×ss Cc

gametic series: SC, Sc, sC, sc | sC, sc

| | SC | Sc | sC | sc |
|---|---|---|---|---|
| sC | 1 Ss CC | Ss Cc | 3 ss CC | 4 ss Cc |
| sc | 5 Ss Cc | 6 Ss cc | 7 ss Cc | 8 ss cc |

| *Phenotypes* | *Squares* |
|---|---|
| Syndactylous and normally pigmented | 1 2, 5 |
| normal digits and Normally pigmented | 3, 4, 7 |
| normal digits and albino | 8 |
| Syndactylous and albino | 6 |

There is thus 1 chance in 8 of such parents producing such a child

There is a simple method of calculating the probability of the appearance of a particular phenotype among a given progeny The probabilities for the various unit characters of which the particular phenotype is built up are multiplied one by the other

Ss × ss = Ss ss
50 per cent. 50 per cent.
Cc×Cc = CC Cc cc
5 per cent. 50 per cent. 5 per cent.

Chance for offspring to be Syndactylous (Ss) = 1/
Chance for offspring to be albinotic (cc) = /4
/8

The laws of gene transmission are thus seen to be the laws " of chance. Chance it is that decides which of two alleles present in the genotype of a heterozygote will enter a particular gamete. Chance decides which ovum will be fertilised by a given spermatozoon. An individual has two genes of each kind and these may be alike or different. These were derived from two sources, paternal and maternal respectively To each offspring each of these two parents transmits one, only one, member of each gene pair Segregation in the case of a heterozygote means the provision of equal numbers of the two alleles and so there must be an equal likelihood for a child to receive either of these. So far it has not been necessary to refer to the sex of an individual when discussing

its characterisation It has not mattered whether the gene in question has been received from male or from female parent or received by son or daughter the effect of the gene has always been the same. Moreover the distribution of the members of one gene pair from parent to offspring has not been affected in any way by the distribution of the members of any other gene pair in so far as genes borne on different chromosomes are concerned Finally which member of a given pair of alleles is received by a particular child from its heterozygous parent is not in any way affected by the distribution of these same genes among previous children born to the same parent.

It will be recognised that the operation of Mendel s second law provides the opportunity for mutant genes which have arisen independently to be brought together Advantage can thus be added to advantage if the mutant genes concerned are better than those from which they have arisen

OTHER INTERNATIONAL PEDIGREE SYMBOLS

= Parents not married, children illegitimate

= Consanguineous marriage

= A woman thrice married

= Fraternal twins

= Identical twins

= Twins uncertain if identical

= Sex unknown

= Number and sex unknown

= Two children sex unknown

= Stillborn male child

= Died in infancy sex unknown

= Examined personally

= Examined not personally but by competent person

Various symbols for use in pedigrees in which several different characters have to be recorded, others can be invented as needs be

## CHAPTER III

### LINKAGE

IF the genes are resident in the chromosomes and if the number of gene pairs exceeds the haploid number of the chromosomes it follows that Mendel's second law cannot always hold. There must be many thousands of genes in the human genotype far more than 24, the haploid chromosome number in man, have already been recognised. Each chromosome must therefore carry more than one gene. If more than one gene is resident in one and the same chromosome then so long as the chromosome remains intact the gene group resident in it must travel together from one generation to the next, must remain linked in inheritance.

*Linkage* is the tendency for two or more pairs of genes to assort together instead of obeying Mendel's second law because they are resident in one and the same chromosome. The number of groups of linked genes—linkage groups—should be the same as the haploid number of chromosomes if all the chromosomes carry genes. The number of linkage groups in man should be 24.

This postulate has been shown to be correct in all instances in which the special genetics of the animal or plant has been sufficiently developed. Moreover the relative sizes of the linkage groups—the listed genes in each—corresponds roughly to the relative sizes of the chromosomes the longer the chromosome the longer the list and the larger the group

The facts of cytology strongly suggest that linkage will rarely be complete. The existence of chiasmata must surely mean that interchange of sections of chromosome material between chromatids derived from homologous chromosomes takes place during the prophase of the first meiotic division of gametogenesis If this is so then blocks of genes must be mutually transferred from one member of a pair of homologous chromosomes to the other

Linkage is disrupted by this *crossing-over* the interchange of linked genes consequent upon a reciprocal transference of

sections of material between chromatids derived from homologous chromosomes.

As yet it is impossible to illustrate at all satisfactorily the phenomena of linkage and crossing-over in the autosomes of man. There are many instances in which because of the behaviour of characters in inheritance linkage is strongly suspected, but it has not so far been confirmed. We must wait awhile. Linkage has shown itself to be so very useful an instrument in genetical enquiry that it is to be hoped that it soon will be recognised in human genetical studies. If two genes are linked and if one corresponds to a deep-seated character of considerable interest and importance affecting viability or functional efficiency for example, whilst the other yields a superficial character readily recognised but of no great importance in itself then so long as the genes remain together the second character can be used as a tracer for the first. The presence of the first could be assumed from the display of the second

It is possible fortunately to illustrate these phenomena by reference to genes resident in the X-chromosome, but before doing so it is desirable to discuss these matters in a general and theoretical way If the genes are resident in the chromosomes, and if each gene has its own appointed place in the length of a particular chromosome, an individual heterozygous in respect of several of these genes can have a genotype of the following kind —

a pair of autosomes $\frac{\text{A B C D E F G H I J K L M N}}{\text{a b c d e f g h i j k l m n}}$

If it be assumed that two chromatids derived from these chromosomes stick, break and reunite with mutual interchange of substance at a point between the loci occupied by the genes E and e and F and f respectively the reconstructed chromosomes will have the following gene content —

$$\frac{\text{A B C D E f g h i j k l m n}}{\text{a b c d e F G H I J K L M N}}$$

The interchange has broken down the spatial relations of the blocks of genes to the left and to the right of the level of crossing-over

Multiple crossing-over can occur recombinations taking place simultaneously at several levels. Double crossing-over in the case of the autosome being considered could give the following result —

$$\frac{A\,B\,C\,D\,E\,f\,g\,h\,i\,J\,K\,L\,M\,N}{a\,b\,c\,d\,e\,F\,G\,H\,I\,j\,k\,l\,m\,n}$$

As a result of such crossing-over combinations of characters exhibited by heterozygous parents are broken down and rebuilt into different combinations in the progeny Manifestly crossing over between two chromosomes containing identical gene companies (in the completely homozygous individual) would cause no such recombination since what each chromatid gave up in interchange it would receive in return

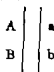
If crossing-over can occur with equal ease at any level in the length of the chromosome, and if crossing-over at any one level renders synchronous crossing-over nearby difficult (*interference*) then it follows that the frequency of crossing-over can be regarded as a rough measure of the distance in the length of the chromosome that separates the two levels involved. There should be a characteristic crossing-over frequency or percentage of crossing-over a *crossing-over value* (C O V), between each two levels. If Aa Bb and Cc are three linked gene pairs their spatial relationship in the chromosome can be represented as points on a line. If this order is $\frac{A\,B\,C}{a\,b\,c}$ then the C.O V between A and C should be the sum of the C.O Vs. between A and B and B and C This is so and it means that the genes are arranged in linear order in th chromosome. For this reason a chromosome map can be constructed showing the genes in their proper order and the distances separating them. The method of map construction is as follows.

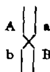
The genes A and B are known to be resident in the same chromosome (linkage) The doubly heterozygous individual's genotype will therefore be

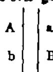
$$\frac{A\,B}{a\,b} \text{ or } \frac{B\,A}{b\,a}$$

This individual will elaborate four kinds of gametes, not two

non-cross-over gametes                                         cross-over gametes




and mated with the double recessive (ab) (ab) will yield the following zygotes —

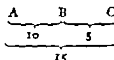
(AB)(ab) (ab)(ab) : (Ab)(ab) (aB)(ab)
non-cross-over classes   cross-over classes

The bracket represents a chromosome and the letters within the bracket the gene company in the chromosome

The majority of the gametes elaborated by the double heterozygote will be non-cross-overs the proportion of cross-over gametes will be determined by the distance in the length of the chromosomes between the levels of A and B Crossing over in the case of the double recessive will not affect the relationship of a and b and the recessive characters cannot confuse the issue. The relative number of the cross-over phenotypes among the progeny gives the C.O V

If for example, each of the non-cross-over phenotypes amounts to 45 per cent. of the total progeny and each of the cross-overs roughly to 5 per cent. then crossing-over occurred in 10 per cent. of instances in gametogenesis The C.O V is 10 per cent. and the levels of A and B (or of course of a and b) are separated one from the other in the length of the chromosome by 10 units of distance.

But is A to the left or to the right of B ? This is a question that can only be answered by recourse to a three-point experiment. A third gene C is shown to belong to the same linkage group It is found that the C O V between A and C is 15 per cent. and between B and C 5 per cent. Then the order must be




And so by obtaining the C.O V between any other gene of this linkage group and any two of the genes already mapped the spatial relationship of all can be determined.

Crossing-over is affected by temperature X-rays radium and certain other chemical and physical agents. It seems probable that these affect the frequency of chiasma formation and that the C.O V is a measure not of the distance between two levels but of the frequency of chiasma formation between these levels However it is a convenience to speak of the C.O V as a measure of distance, 1 per cent. indicating that the two levels concerned are separated by one unit of distance. The ease with which crossing-over occurs differs between the sexes in many species In certain forms there is no crossing over in one sex, linkage being complete. But this cannot mean that the chromosome has no physical length it merely means that for reasons as yet unknown crossing-over does not occur In man crossing-over would seem to occur with equal ease in both sexes

## Sex linkage

The X and the Y chromosomes like the autosomes are the vehicles of gene groups. But owing to the heterogametic nature of the human male and therefore to a sex difference in respect of the sex-chromosomes the transmission of the X and the Y-borne genes differs from that of the genes resident in the autosomes

It is not to be understood that because a gene is resident in a sex-chromosome it is therefore necessarily specially or mainly concerned in the production of sex or of the sexual characters They are called sex linked solely because they are resident in a pair of chromosomes in respect of which the sexes differ and which are involved in sex determination. The male receives his Y-chromosome from his father his X from his mother the female receives an X from each parent.

The essential difference between the sex-chromosomes and the autosomes is that the X and the Y do not in their entirety constitute a pair of homologous chromosomes. Only parts of them are homologous being built up of the same gene material. These portions or sections pair and between them crossing-over takes place But the greater part of the X and the rest of the short Y are non-homologous between these there is no pairing, no interchange. The genes in these sections remain completely

X-borne or Y borne, the genes of the non-homologous portion of the Y being the peculiar property of the male.

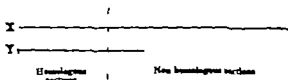



FIG. 7.—Diagram of the sex-chromosomes, showing the homologous and non-homologous portions

Because there are (1) homologous sections of the X and Y (2) a non homologous section of the Y and (3) a non-homologous section of the X there must be three kinds of sex linked inheritance.

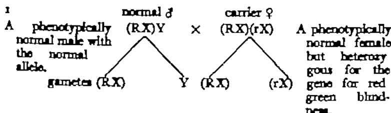
1 Total sex-linkage Genes resident in the *non homologous* portion of the X and restricted to the X.
2 Total sex-linkage. Genes resident in the non homologous portion of the Y and restricted to the Y
3 Partial sex-linkage. Genes resident in the homologous sections of the X and the Y partial because crossing over can disrupt linkage

## TOTAL SEX LINKAGE. GENES RESIDENT IN THE NON HOMOLOGOUS PORTION OF THE X

Red-green blindness, the inability to recognise these colours, is a sex-linked recessive character the gene for which is resident in the non-pairing segment of the X-chromosome. It is to be found in some 4 per cent. of males and 0 4 per cent. of females of our population. Since most red and green colours used in signals and such like are not monochromatic the condition is not regarded as a serious disability in most occupations. Scores of red-green blind individuals remain completely unaware of their peculiarity

Since the gene is X borne and cannot be transferred through crossing-over to a Y and since it is a recessive, the heterozygote can be none but a female. A male can either have this gene on his X when he will be red-green blind or else he can have the normal allele on his X, when he will be normal sighted There is no locus for these genes in his Y

The following matings can occur —



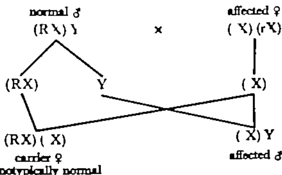

| ♀ \ ♂ | (RX) | Y |
|---|---|---|
| (RX) | 1 (RX)(RX) | 2 (RX)Y |
| (rX) | 3 (RX)(rX) | 4 (rX)Y |

Square 1 Phenotypically and genotypically normal ♀.
Square 2 Phenotypically and genotypically normal ♂
Square 3. Phenotypically normal ♀ but heterozygous for the red-green blindness gene.
Square 4 Affected ♂

Expected, ratio of normals to affecteds = 3 : 1

Equal numbers of ♂♂ and ♀♀, of normal and carrier ♀♀, of normal and affected ♂♂

According to this scheme the child, to be a male must receive his Y-chromosome from his father From his mother he receives his single X. The mother has two kinds of Xs Should the son receive the one carrying the recessive allele he will be affected.

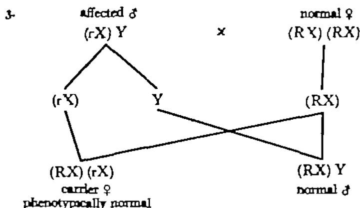



Expected, equal numbers of normals and affecteds.

Equal numbers of ♂♂ and ♀♀, the former all affected, the latter all carriers.

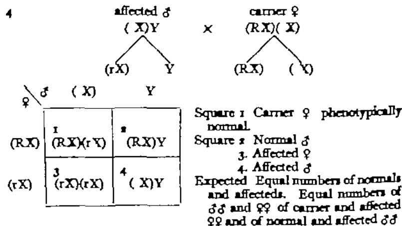
Male offspring must be affected since the mother can offer only one kind of X the one with the recessive gene. Note

that in this pedigree the sons take after their mother and the daughters take after their father. This is an instance of *criss-cross inheritance*. It is seen that in dealing with sex linked genes it is necessary to state the sex of the individual as well as the character the individual displays.




Expected, all normals but daughters are carriers.
Equal numbers of ♂♂ and ♀♀

Sons must be normal for the reason that the mother can offer only one kind of X that with the normal allele. Daughters must be carriers because the X they receive from their father carries the recessive gene.

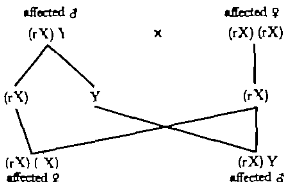



| ♀ \ ♂ | ( X) | Y |
|---|---|---|
| (RX) | 1 (RX)(rX) | 2 (RX)Y |
| (rX) | 3 (rX)(rX) | 4 ( X)Y |

Square 1 Carrier ♀ phenotypically normal.
Square 2 Normal ♂
3. Affected ♀
4. Affected ♂
Expected Equal numbers of normals and affecteds. Equal numbers of ♂♂ and ♀♀ of carrier and affected ♀♀ and of normal and affected ♂♂

The mother has two kinds of Xs therefore there will be two kinds of sons. The father's X carries the recessive gene, therefore there will be two kinds of daughters, affecteds and carriers.

5




Expected, all affecteds.
Equal numbers of ♂♂ and ♀♀.

Certain characteristic features of total sex linked inheritance are presented in these results Reciprocal matings yield different results (matings 2 and 3). Segregation can differ between the sexes (mating 2) Segregation among males is determined solely by the genotype of the mother independent of that of the father A male showing the dominant character and a female with the corresponding recessive produce sons showing the recessive and daughters with the dominant—criss-cross inheritance—(mating 2) A male with the recessive character and a female with the corresponding dominant in the homozygous condition produce offspring all with the dominant, but all the daughters are heterozygotes (mating 3) An affected male transmits *the gene* to all his daughters but to none of his sons A carrier female transmits it—the gene—to half of her sons and to half of her daughters when mated with a normal male (mating 1) and to half of her sons and to all of her daughters when married to an affected mal (mating 4) An affected femal transmits it to all her offspring regardless of the genotype of her husband (matings 2 and 5).

Fig 8 shows a pedigree of red-green blindness.

I must have been a carrier since there are affected females in II II$_2$, being affected is necessarily a homozygote. II and II$_4$ are carriers III$_3$ is a carrier

One form of hæmophilia furnishes another example of a character based upon a recessive gene resident in the non pairing segment of the X-chromosome. As long ago as 1803 Dr J hn Otto of Philadelphia had recorded of hæmophilia

that males only are affected and all are not liable to it Though females are free they are capable of transmitting it to their children. Its mode of inheritance is exactly similar to that of red-green colour blindness but it is a much more serious condition. The affected individual bleeds profusely from the slightest cut the eruption of teeth becomes a dangerous adventure and minor operations such as tooth extraction or tonsillectomy are attended with dread since clotting is greatly retarded Slight contusions can give rise to severe bruising and extensive subcutaneous hæmorrhage. Effusions of blood into joints can incapacitate. The life expectancy of such

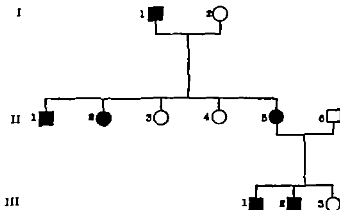
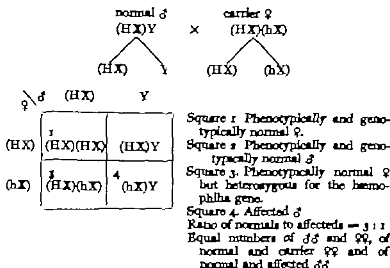



FIG. 8 —Pedigree of Red-green blindness, totally sex linked recessive, determined by gene in the non-homologous segment of the X

individuals is greatly reduced On the average hæmophiliacs produce only about a quarter as many children as do normals. Affected males are usually removed by death before the age of twenty five. They beget but few offspring therefore. For this reason alone female hæmophiliacs must be rare since to be a hæmophiliac a female must have had a hæmophiliac for a father In pooled pedigrees of hæmophilia there is a significant deficiency of females and it would seem that the homozygous female commonly dies *in utero*

It is of particular interest to note that in the Talmud sanction is given for the omission of the ritual of circumcision in the case of sons of women regarded as being likely to produce hæmophilic offspring

It is the marriage of a normal male with a carrier female that provides the overwhelming majority of hæmophiliacs in a human community




It is important to note that in respect of these genes there are three kinds of females, normals, carriers and affected, and only two kinds of males normals and affected The danger comes from the carrier in our midst. A female is certainly a carrier if her father was affected. A female is certainly a carrier if she belongs to a hæmophilic family and produces an affected son if she produces no sons it is impossible to say that according to the genetic evidence she is a carrier It *now seems to be possible, by the use of techniques recently* developed, to detect the heterozygous female by a characteristic coagulation time of her blood. If the frequency of hæmophilic males among the male population is $p$ and the frequency of normal males is $q$ where $(p+q) = 1$ then with random mating the frequency of hæmophiliacs carriers and normals among the female population is $p^2$ $2pq$ $q^2$

Queen Victoria was heterozygous for the hæmophilic gene. The mutation giving rise to this gene would appear to have occurred during spermatogenesis in her father the Duke of Kent Among her descendants there have been one hæmophilic *son, at least three* hæmophilic grandsons and six hæmophilic

D

great-grandsons Edward VII was normal and since neither he nor his descendants married into families with a history of hæmophilia the House of Windsor is free from this sex linked

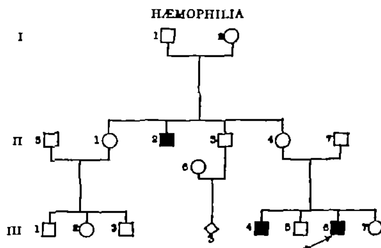



FIG. 9.—Pedigree of Hæmophilia, totally sex linked recessive, determined by gene in the non-homologous segment of the X

I is carrier II is possibly normal, her children are too few to make it certain that she is. II is carrier

recessive gene. The Tsarevitch Alexis was a hæmophiliac and it was because of this that the monk Rasputin came to occupy so prominent a position in Russian court circles. It was claimed that he could control the processes of coagulation perhaps by hypnosis. The heir apparent to the throne of Spain is a hæmophiliac and his mother a descendant of Queen Victoria, is a carrier These genetical facts have undoubtedly played their part in determining the destinies of monarchies since illness of this kind is so easily interpreted as the curse of a deity

A dominant sex-linked gene X-borne in the non-pairing segment, yields a character that is commoner in the female than in the male for the reason that she has two X-chromosomes to the male s one and has therefore a much greater opportunity for receiving the gene from one or other of her parents The male gets his single X from one parent, his mother Dominant sex linked inheritance, like dominant autosomal inheritance, is inheritance from one parent. All affected have an affected

parent (in a pedigree this vertical distribution will extend up to the point at which the mutation occurred) The character is exhibited by approximately half the offspring of an affected person. This dominant sex linked inheritance is to be distinguished from dominant autosomal transmission by the fact that in the former affected males mated to unaffected females have only affected daughters and normal sons

$$(AX)Y \times (aX)(aX) = (AX)(aX) \quad (aX)Y$$

whilst in the latter all the offspring irrespective of their sex, are affected ($AA \times aa = Aa$) or if the father is a heterozygote, equal numbers of affecteds and unaffecteds irrespective of sex ($Aa \times aa = Aa \quad aa$)

Congenital absence of the incisor teeth would seem to be such a dominant sex-linked character Defective enamel of the teeth would appear to be another

CONGENITAL ABSENCE OF INCISORS

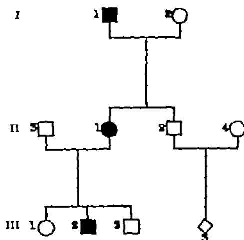
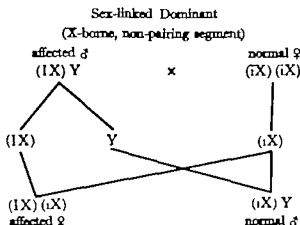


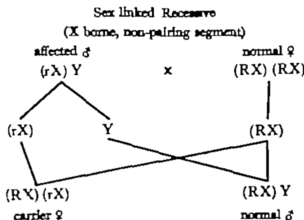

FIG. 10.—Pedigree of Congenital Absence of the Incisors, totally sex-linked dominant, determined by gene in the non-homologous segment of the X

This pedigree by itself is not sufficient to prove that the condition is a sex linked dominant. $I_1$ and $I_2$ did not produce enough children to show that the males of II were invariably normal whilst the females were invariably affected There were only two individuals one a male and the other a female. But

if this pedigree is pooled with others of the same kind then it assumes an importance for the reason that the evidence it provides supports the contention that congenital absence of incisors can, in certain instances, be caused by a dominant sex-linked gene.

It is of interest to compare this pedigree with certain of the matings that were considered in the case of the recessive sex linked character red-green colour blindness.




In the case of red-green blindness criss-cross inheritance was encountered in the mating of a normal male (RX)Y with an affected female (rX)(rX). Amongst the progeny sons were affected like their mother and daughters (phenotypically)

normal like their father In the case of the dominant sex linked character congenital absence of incisors, the mating affected male (IX)Y × normal female (iX)(iX) gave criss-cross inheritance of a different kind for father and daughters were affected and mother and sons normal.

The mating normal male (iX)Y and affected (heterozygous) female, (IX)(iX) yields results that are indistinguishable from that of the back-cross of an ordinary autosomal heterozygous dominant, ptosis (Pp) for example, to the recessive parental form (pp)

Sex linked Dominant

normal ♂ × affected ♀ (heterozygous)

(iX)Y × (IX)(iX)

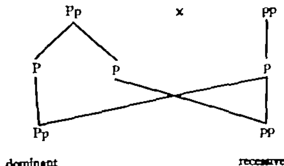



| ♀ \ ♂ | (iX) | Y |
| --- | --- | --- |
| (IX) | 1 (IX)(IX) | (IX)Y |
| (iX) | 3 (iX)(iX) | 4 (iX)Y |

Square 1 Heterozygous affected ♀.
2 Affected ♂
" 3. Normal ♀
4. Normal ♂

Equal numbers of males and females.
Equal numbers of normals and affecteds.

Autosomal Dominant




dominant recessive

Equal numbers of the two phenotypes and equal numbers of ♂♂ and ♀♀

Genes resident in the non-homologous part of the X chromosome are linked with one another Since the female

has two such portions, one in each X crossing-over between the two portions is possible. Such crossing-over cannot take place in the male who has only one such section of the X

A female who is doubly heterozygous in respect of the genes for red-green colour blindness and for hæmophilia therefore should provide the opportunity for the study of linkage and crossing-over Her genotype can be represented so

$$\frac{+h \qquad +r}{h \qquad r} \quad \text{or} \quad \frac{+h \qquad r}{h \qquad +r}$$

or (HRX)(hrX) (HrX)(hRX)

that is to say the two mutant genes can be together in one X and the two normal alleles in the other or there can be one mutant gene and one normal allele in each of the Xs If the two mutant genes are in the same chromosome they show the tendency to remain together in transmission (the phenomenon known as *coupling*) If they are in separate chromosomes they show a tendency to remain apart (the phenomenon of *repulsion*) The two kinds of distribution of these four genes among the two chromosomes yield different results

(A)

Normal ♂ $\begin{matrix} X \\ Y \end{matrix} \ \frac{+h \quad +r}{\rightharpoondown} \times \frac{+h \quad +r}{h \quad r}$ a phenotypically normal but doubly heterozygous ♀

| Progeny | $\frac{+h \quad +r}{+h \quad +r}$ | $\frac{+h \quad +r}{h \quad r}$ | $\frac{+h \quad +r}{\rightharpoondown}$ | $\frac{h \quad r}{\rightharpoondown}$ |
|---|---|---|---|---|
| | normal ♀ homozygous for both +h and + | normal ♀ but doubly hetero-zygous | normal ♂ | hæmophilic and red green blind ♂ |

(B)

Normal ♂ $\frac{+h \quad +r}{\rightharpoondown} \times \frac{+h \quad r}{h \quad +r}$ phenotypically normal but doubly heterozygous ♀

| Progeny | $\frac{+h \quad +r}{+h \quad r}$ | $\frac{+h \quad +r}{h \quad +}$ | $\frac{+h \quad r}{\rightharpoondown}$ | $\frac{h \quad +r}{\rightharpoondown}$ |
|---|---|---|---|---|
| | normal ♀ homozygous for +h, hetero-zygous for | normal ♀ homozygous for + hetero-zygous for h | red-green blind ♂ but not hæmophilic, 50 per cent of the sons | hæmophilic ♂ but not red-green blind, 50 per cent of the sons |

All this of course, in the absence of crossing-over between the Xs of the female This would disturb the spatial relationship

of the genes concerned and so yield different combinations of characters in the male progeny so —

(C) Crossing-over affecting Case A above.

Normal +h +r / ⌐ × +h +r / h r phenotypically normal but doubly heterozygous

+h r / h +r crossing-over

+h r / h +r cross-over gametes

Progeny

| +h +r / +h r | +h +r / h +r | +h r / ⌐ | h +r / ⌐ |
|---|---|---|---|
| normal ♀ but heterozygous for r | normal ♀ but heterozygous for h | red-green blind but not haemophilic ♂ | haemophilic but not red-green blind ♂ |
| | | cross-over phenotypes | |

(D) Crossing-over affecting Case B above.

Normal ♂ +h +r / ⌐ × +h +r / h r phenotypically normal but doubly heterozygous ♀

+h r / h +r

+h r / h +

| +h + / +h r | +h +r / h +r | +h r / ⌐ | h +r / ⌐ |
|---|---|---|---|
| normal ♀ but heterozygous for r | normal ♀ but heterozygous for h | red-green blind ♂ but not haemophilic | haemophilic ♂ but not red-green blind |
| | | cross-over phenotypes | |

The two recessive genes on the X of the female are thus separated with the result that cross-over classes appear as well as non-cross-overs among the male progeny

The C.O.V. between the two loci has been shown to be in the region of about 11 per cent. The two genes therefore lie close together in the length of the chromosome. More than this cannot be said until several more genes of this group have been mapped together with these two The gene for one form of optic atrophy would seem to belong to this group

## TOTAL SEX LINKAGE. GENES RESIDENT IN THE NON HOMOLOGOUS SECTION OF THE Y-CHROMOSOME

Such genes as are carried in this non-pairing segment of the Y are passed directly from father to son (holandric inheritance). They affect characters that are restricted to the male. Webbed toes has been recorded as a gene of this kind. Here is a pedigree involving this condition.

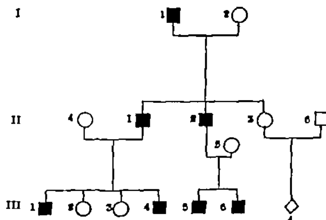



FIG. 1.—Pedigree of Webbed Toes, totally sex-linked character determined by gene in the non-homologous portion of the Y

Every male is affected all females are normal. Every male transmits the abnormality to all his sons and to none of his daughters. To follow the character through the generations is to trace the Y-chromosome and the gene in its non-pairing segment.

Manifestly such a sex-linked character has to be distinguished from what is known as a sex limited sex influenced or sex-controlled character. Hypospadias (the condition in which the urethra as the result of developmental imperfection opens on the under surface of the penis instead of at the distal end) is a genetic character its gene being an autosomal dominant. The female cannot exhibit this character her anatomy makes this impossible. It is therefore restricted to the male. Congenital dislocation of the hip is a genetic character that finds expression more frequently in the female for anatomical reasons. Genes if there be such in the human

subject, affecting the quantity and quality of milk can find expression only in the female. Pattern baldness starting at the crown and temples in early manhood and quickly spreading over the whole of the top of the head, is a genetic character. Its autosomal gene must find itself it would seem, in a male internal (endocrinological) environment if it is to gain full expression. This gene is of interest in that the sex of its possessor affecting as it does the expression of the character destroys the dominance-recessiveness relationship of this gene and its normal allele. One gene causes pattern baldness in the male, two of them are required to produce even sparseness or partial baldness in the female. If the male is heterozygous and the woman normal half the sons of the marriage will develop the character if the male is homozygous all his sons will do so If the woman is a heterozygote and is married to a normal male half her sons will show the character If she is a homozygote she will have sparse hair and in later life partial baldness and all her sons will develop the character Male and female differ one from the other in respect of hair characters but it is difficult to find any reason why the gene for webbed toes should operate only in a male environment and to judge by the pedigree its gene must be Y-borne. Sex limitation is restricted to sex-dimorphic characters—those by which the sexes are to be distinguished—and so is unlikely to be confused with sex linkage.

There are several genes which find it easier to gain expression in the male rather than in the female internal environment. Multiple exostoses (bony outgrowths from the surface of a bone) are found about twice as often in men as in women Its gene is an autosomal dominant and affected fathers produce both affected sons and affected daughters. One form of oligophrenia (imbecility) and the Laurence-Moon Biedl syndrome (mental deficiency obesity hypogenitalism polydactyly and retinal degeneration) are both encountered far more frequently in the male than in the female. Yet both are based on autosomal recessive genes.

## PARTIAL SEX LINKAGE

Genes resident in the homologous or pairing segments of the X and Y-chromosomes can become transferred

through crossing-over from the X to the Y or *vice versa* This being so it follows that these genes will not always remain linked. Moreover since any one of these genes can be transferred from the X to the Y or from the Y to the X it can be possessed by male and female alike.

Because of this crossing-over these genes will give every appearance of being autosomal borne, and in fact from the point of view of the clinician it is enough that they shall be so regarded It is only when an unusual sex-distribution of the character being considered is recognised that the evidence for partial sex linkage is revealed In some families showing a particular condition affected males will be found to be much rarer than was to be expected In others there will be fewer affected females than there should have been if autosomal inheritance were concerned. It is only by the analysis of individual family records that the existence of partial sex linkage has been detected When pooled pedigrees of this kind are examined the unusual sex-distribution of one kind in certain families is balanced by an unusual sex-distribution of the other kind so that in such studies the mode of inheritance would seem to be entirely autosomal and the genes autosomal borne.

A male who has received the recessive gene from his father will carry it in his Y-chromosome and will therefore transmit it mainly to his sons but as a result of crossing-over a few exceptional daughters will receive it also. A male who has received the gene from his mother will carry it in his X chromosome and will therefore transmit it to his daughters, but as a result of crossing-over it will pass also to a few exceptional sons.

The essential difference between partially sex linked and autosomal transmission is as follows A male who receives a partially sex-linked gene from his father transmits it to more than half of his sons and to less than half of his daughters, whilst if he receives it from his mother he transmits it to less than half of his sons and to more than half of his daughters This unusual distribution of sex and character in association is the result, of course, of crossing-over between the X and the Y

Seven genes previously looked upon as autosomal genes

are now suspected to be partially sex-linked. They are the genes for

| | | |
|---|---|---|
| Retinitis pigmentosa | dominant | alleles |
| Retinitis pigmentosa (without deafness) | recessive | |
| The malignant form of epidermolysis bullosa | a recessive | |
| Spastic paraplegia | recessive | |
| Oguchi' disease ( form of night-blindness) | recessive | |
| Xeroderma pigmentosum | recessive | |
| Achromatopsia (total colour blindness) | recessive | |

Retinitis pigmentosa is among the commonest of genetic abnormalities. It takes the form not of an inflammation as the name would suggest, but of a gradual degeneration of the retina commencing usually in infancy or childhood (although exceptionally being delayed until early adult life) The first symptom is night blindness, readily to be distinguished from congenital stationary night blindness, an autosomal dominant character which is present at birth and not progressive. There is progressive contraction in the visual field and finally blind ness Ophthalmoscopic examination of an advanced case shows the vessels of the fundus to be reduced in size with jet black spidery spots of pigment lying on them. The retina and choroid are atrophied and the disk waxy in appearance.

Epidermolysis bullosa is a condition in which blisters form as the result of injuries so trivial that they would produce no effect whatsoever in the normal individual. In the severest form whole areas of skin may be absent at birth and blistering occurs in the mouth and larynx, bronchi and oesophagus and the cornea and conjunctiva may be affected. The teeth may be abnormal.

Spastic paraplegia, a series of clinical conditions dependent upon imperfection in development or on degeneration of the nerve cells of the cerebral cortex, basal ganglia or cerebellum, is remarkable for muscular rigidity paresis perverse movements, contractures, increased reflexes and is associated with mental deficiency optic atrophy and ataxy It is displayed during the first year of life.

Oguchi s disease is a form of night-blindness which is to be recognised by a curious golden appearance of the fundus when this is adapted to light. This disappears when the fundus is adapted to darkness

Xeroderma pigmentosum is a condition in which in an infant a few months old there is profuse reddening of the skin

of parts exposed to ordinary sunlight. Freckles develop, enlarge and deepen in pigmentation. Warts and patchy atrophy of the skin follow Corneal ulcers lead to opacities. Basal-celled carcinomata arise in the skin, conjunctiva and cornea. The gene kills the child just as surely as does the larva of the igneumon fly destroy its caterpillar host

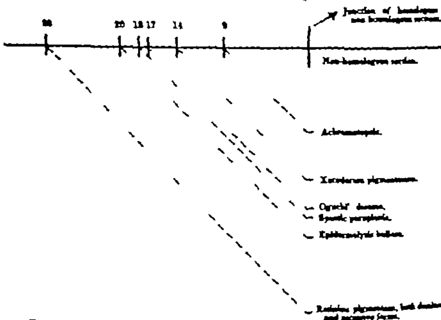



FIG. 12.—Diagram of the homologous segment of the X, showing the genes resident therein. The map of the human X-chromosome

Achromatopsia, congenital total colour blindness, is a rare condition in which the individual sees practically no colour at all. Everything appears to be black, white or a shade of grey Usually there is associated amblyopia, nystagmus and photophobia.

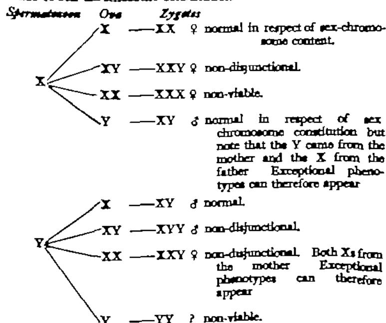
The disturbed proportions of the excepted phenotypes by the appearance of cross-overs within each family exhibiting any two of the characters based upon these genes makes it possible to place them tentatively in their relative positions in the homologous sections of the X and the Y

## NON-DISJUNCTION

Abnormal distribution of the X-chromosomes during the meiotic divisions of oögenesis of the mother can yield exceptional phenotypes among the offspring Normally into each ovum there passes one member of the XX pair of chromosomes.

But occasionally during that division which yields the ovum and the polar body these XXs fail to separate, to disjoin, and both pass into the ovum or else into the polar body This phenomenon is known as *non-disjunction* of the sex-chromosomes. In certain instances this non-disjunction results from the fact that the two Xs are actually attached and cannot separate. Such an XX ovum is available for fertilisation by an X or a Y spermatozoon. Resulting from fertilisation an XXY or an XXX zygote can appear The former will be a female—it has two X-chromosomes and the Y does not exert sufficient influence to disturb the result. The latter is a zygote that apparently is not viable.

Oögenesis in an XXY female will be complicated by the necessity for disjunction to separate the X and the XY or the XX and the Y In respect of sex-chromosome content she *will elaborate four kinds of ova instead of one. These will* contain the following sex-chromosomes X XY XX and Y respectively These can be fertilised by an X-bearing or by a Y-bearing spermatozoon to yield zygotes with the following kinds of sex-chromosome constitution —




If a woman with sex-linked red-green colour blindness

happened to have the sex-chromosome constitution XXY the two Xs being attached so that where one goes the other must, and produced children by a homozygous normal sighted man there would appear in addition to the usual normal daughters and affected sons (criss-cross inheritance) exceptional normal sons and exceptional affected daughters

non disjunctional ♀ with attached XXs, affected.

Normal ♂ (RX)Y × (rX)(rX)Y

Gametes (RX) Y (rX)(rX) Y

Progeny (RX)(rX)(rX) a triplo-X female affected (?) non-viable (?)

(RX)Y a normal male X from father *Y from mother*

(rX)(rX)Y an affected female XXY *Both XXs from mother*

YY non viable.

If the triplo-X female and the YY zygote do not appear there will be equal numbers of males and females among the

RED-GREEN BLINDNESS

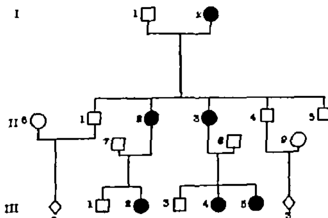
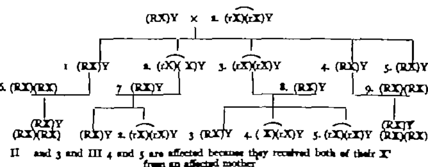



FIG. 13.—Pedigree of Red-green blindness, peculiar by reason of the attached Xs in an affected XXY female

progeny normal sons like their father and affected daughters like their mother a mode of inheritance that cannot be accommo-

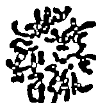
dated by the normal chromosome distributing mechanism. The aid of non-disjunction must be invoked




II and 3 and III 4 and 5 are affected because they received both of their X' from an affected mother

In the case of a dominant X-borne gene such as that for the dominant form of retinitis pigmentosa the attached XXs of an XXY female could disturb the sex incidence of the condition among the offspring a son of an affected mother homozygous) (AX)(AX)Y by a normal father (aX)Y could be normal by receiving his father's X and his mother's Y The expected result of such a mating with non-attached Xs is affected sons and daughters (heterozygous).

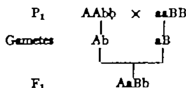
$$(aX)Y \times (AX)(AX) = (AX)(aX) \quad (AX)Y$$



## CHAPTER IV

### MULTIPLE ALLELOMORPHS

IT will not have escaped notice that on the map of the non pairing segment of the X-chromosome two mutant genes were placed in one and the same locus those for the dominant and for the recessive form of retinitis pigmentosa respectively They were placed there for the reason that the C O Vs between either of them and any other gene in the group were identical. Unless they are resident in loci so close together as to be indistinguishable these genes must therefore be allelomorphic to each other and also to the unmutated normal gene from which they arose. If this is so then a gene must be able to mutate in several ways to yield several allelomorphs This is so. A gene and its several mutant forms constitute a *multiple allelomorphic series* of which not more than two members can be present in the genotype of any one individual Such a series usually controls a given character or set of characters quantitatively so that they can be arranged in a series according to the degree to which the effects diverge from the normal. Usually also the unmutated gene is dominant to all the rest. When two different alleles are present together they usually yield an intermediate effect It is this intermediacy of the compound that is characteristic of a multiple allelomorphic series and distinguishes its members from ordinary recessives. If an individual displaying one recessive character is mated with another exhibiting a different recessive the offspring will be doubly heterozygous and will display the two corresponding dominants so —



This is not the case with the members of a multiple allelomorphic series.

## THE A, B AB AND O BLOOD GROUPS

The autosomal genes which underlie the A, B O blood groups are members of such a series. There are four blood groups referred to as A, B AB and O respectively These groups differ one from the other in respect of the antigens and antibodies present in the blood. The antigens are known as the A and B antigens the antibodies as anti A and anti B respectively Finally the genes responsible for the differences in respect of these antigens and antibodies have been given the symbols A, B and O No wonder the geneticist reading the literature on this subject commonly finds himself in doubt as to whether the As and Bs and Os which he encounters refer to the blood groups, the antigens or to the genes. And now that this nomenclature is in common use in clinical medicine it is too late so to amend it that it will conform to genetical convention. But for the purposes of this book it is necessary to make the attempt.

| *The phenotype* | | *The gene(s) responsible* |
|---|---|---|
| Blood group A | Presence of antigen A in the red blood corpuscles. Presence of antibody anti B in the serum. | $H^A$ |
| Blood group B | Presence of antigen B in the R.B Cs. Presence of antibody anti-A in the serum. | $H^B$ |
| Blood group AB | Presence of antigens A and B in the R.B Cs. Absence of antibodies anti A and B in the serum. | $H^A$ and $H^B$ conjointly |
| Blood group O | Absence of antigens A and B in the R.B Cs. Presence of antibodies anti A and anti-B in the serum. | $H^O$ |

In accordance with genetical convention one and the same initial letter is used for every allele (H = human antigen and antibody) and one allele is distinguished from the others by the addition of a suffix. It will be noted that where there is antigen A there is no anti A antibody where there is antigen B there is no anti B antibody and that wherever antigen A

is absent antibody anti A is present and wherever antigen B is absent antibody anti-B is present. These are the important observations that have determined blood transfusion practice. In this the danger is in the introduction from a donor of red blood corpuscles containing an antigen or antigens which will be attacked by the antibodies present in the blood plasma of the recipient.

Blood group typing consists of testing an individuals R.B Cs against sera of known antibody content An individual is placed in group A if his erythrocytes are agglutinated by serum containing antibody anti-A but not by serum containing antibody anti B he belongs to group B if his R.B Cs are agglutinated by serum containing antibody anti B but not by anti A serum he is classified as AB if sera containing anti A and anti B respectively both cause agglutination. If neither of these sera produce agglutination of his R.B Cs then he is placed in group O

Transfusion of whole blood therefore observes the rules indicated in the following table —

*Recipient*

| *Donor* | A<br>anti B | B<br>anti-A | AB<br>neither | O<br>both | antigens<br>antibodies |
|---|---|---|---|---|---|
| A | + | — | + | — | |
| B | — | + | + | — | |
| AB | — | — | + | — | |
| O | + | + | + | + | |

\+ transfusion permissible.

— transfusion not permissible since agglutination results.

The three autosomal genes $H^A$ $H^B$ and $H^O$ form a multiple allelomorphic series. A is dominant to B and O B is recessive to A and dominant to O But dominance is not complete and the compound AB reveals the effect of the action of both

genes. Every individual possesses two out of these three genes. The following genotypes are possible —

| *Phenotype* | *Frequency (per cent) in our population* | *Genotype* |
|---|---|---|
| A | 42·2 | $\frac{A}{A}$ or $\frac{A}{O}$ |
| B | 8·7 | $\frac{B}{B}$ or $\frac{B}{O}$ |
| AB | 3 | $\frac{A}{B}$ |
| O | 45·8 | $\frac{O}{O}$ |

Recently the gene $H^A$ has been shown to exist in three allelomorphic forms differing in respect of the intensity of the action of the antibody anti A on the A antigen, strong medium and weak, the strong being dominant to the medium and the weak and the medium to the weak. The multiple allelomorphic series consists therefore of five members $A^1$ $A^2$ $A^3$ B and O

Possessing this purely genetical information it is possible to predict the possible phenotypes and genotypes of the offspring to be expected from any given mating

| | | *Phenotypes* |
|---|---|---|
| $\frac{A}{A} \times \frac{A}{A} =$ | 00 per cent. $\frac{A}{A}$ | 100 per cent. A |
| $\frac{A}{A} \times \frac{A}{O} =$ | 5 per cent. $\frac{A}{A}$ | 100 per cent. A |
| | 50 per cent. $\frac{A}{O}$ | |
| $\frac{A}{O} \times \frac{A}{O} =$ | 5 per cent. $\frac{A}{A}$ | |
| | 5 per cent. $\frac{A}{O}$ | 75 per cent. A<br>25 per cent. O |
| | 25 per cent. $\frac{O}{O}$ | |

and so on throughout the series, t being remembered that no more than two of the five alleles can be possessed by any one individual and that $A^1$ is the top of the series and O the bottom.

| *Phenotypes of parents* | *Possible phenotypes of offspring* | *Phenotypes lacking among offspring* |
|---|---|---|
| A×A | A, O | B AB |
| A×B | A, B AB O | — |
| A×AB | A, B AB | O |
| A×O | A, O | B AB |
| B×B | B O | A AB |
| B×AB | A, B AB | O |
| B×O | B O | A, AB |
| AB×AB | A, B AB | O |
| AB×O | A, B | AB O |
| O×O | O | A, B AB |

It is possible by the employment of special techniques to demonstrate the presence of these A and B antigens in the saliva of about 80 per cent. of the population This property is based on an autosomal dominant gene, S

### The M and N Antigens

Human erythrocytes have been shown to contain two antigens to which the symbols M and N respectively have been attached Every individual has one or the other or both of these and they are never simultaneously absent. But human serum does not contain (save very exceptionally it now seems) an anti M or an anti N antibody so that these matters are of no concern in blood transfusion. The antibodies are produced by the injection of human R.B Cs with one or other of the M and N antigens into rabbits Rabbit sera thus prepared is then used for the detection of the M and N antigen characters in human blood

The phenotypes M = the presence of M antigen N = the presence of N antigen, MN = the presence of both antigens are based on a pair of genes, $R^M$ and $R^N$ resident in an autosome other than that in which the ABO series is found Between M and N there is no dominance and the heterozygote MN shows the effect of both

| *Phenotype* | *Frequency (per cent) in our population* | *Genotype* |
|---|---|---|
| M | 29·7 | $\frac{M}{M}$ |
| N | 21·2 | $\frac{N}{N}$ |
| MN | 49·0 | $\frac{M}{N}$ |

The following matings are possible and they will yield the following phenotypes among the progeny

| *Phenotypes of parents* | *Possible phenotypes among offspring* | *Phenotypes lacking among offspring* |
|---|---|---|
| M×M | M | N MN |
| M×N | MN | M, N |
| M×MN | M, MN | N |
| N×N | N | M MN |
| N×MN | N MN | M |
| MN×MN | M N MN | — |

Recently an allele of N $N_2$, giving a weaker effect than N has been identified. It seems therefore that the M $N_1$, $N_2$ genes form yet another multiple allelomorphic series. Since the ABO series and the MN pair of genes are on different autosomes the mode of inheritance of the characters will be in accordance with Mendel s second law of independent assortment.

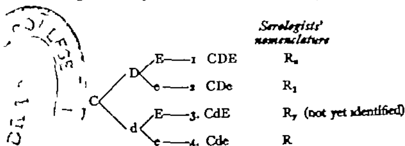
In the course of this anti-M antibody work another anti body anti-P was discovered which disclosed the presence of another antigen, P in human red blood corpuscles. P is present in approximately 75 per cent. of the population. It is based on an autosomal dominant gene, P So far there is no conclusive evidence that the P factor is of any importance in blood transfusion there is as yet no record of a haemolytic transfusion reaction due to anti P antibodies. But there are suggestions that there have been obstetrical disasters in cases in which the father was P positive the mother P-negative.

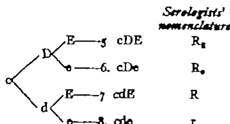
### The Rhesus Antigens

By injecting the red blood corpuscles of the Rhesus monkey into guinea pigs and rabbits it was found possible to obtain serum that contained antibodies which injected into the human subject, revealed the presence in human erythrocytes of certain antigens—the so-called Rhesus antigens. Individuals whose erythrocytes are agglutinated by these antibodies are said to be Rhesus (or Rh or R) positive those in whom this reaction does not occur are Rhesus negative. Eighty-five per cent. of our population is R+ 15 per cent. R− (with reference to the first discovered and still most important D antigen). The importance of these discoveries lies in the fact that in

*about 90 per cent. of instances of erythroblastosis foetalis* (incidence about 1 in every 200 pregnancies) the cause is a difference between the parents in respect of these Rhesus properties the mother being R– the father and the infant R+ More than six Rhesus antigens have already been identified but for the moment only six will be considered To these the symbols C c, D d E e have been given. Every human individual carries at least three of these in his erythrocytes some have four five or even all six. The corresponding antibodies anti-C anti-c, etc. are never spontaneously formed in any human serum. But an individual lacking a particular antigen *may* develop the corresponding antibody if he receives a blood transfusion including erythrocytes containing that antigen. Usually one such transfusion is not sufficient to produce this reaction, several are necessary A pregnant woman lacking a particular antigen and carrying a foetus possessing it, having received it by way of the spermatozoon *from his father may develop in her serum the corresponding* antibody This then may react with the erythrocytes of the foetus to cause erythroblastosis foetalis The antibody develops slowly so that it may not be the first born but subsequent foetuses that are affected.

These six antigenic characters would appear not to be based on single genes each antigen apparently rests on a group of three genes resident in loci very close together in the length of an autosome. Because they lie so close together in the length of the chromosome crossing-over between any two of them will be a very rare event. It may be that the rarer gene associations are the results of such crossing-over There is no dominance among them each gene and gene group produces its own effect irrespective of the action of all the rest. These six genes can provide the following gene groups —






Gene groups 2 8 and 5 in this order are the commonest in our population being possessed by some 95 per cent. of the whole. Every human being has two of these eight gene groups and they may be the same or different. There are thus thirty-six ways in which these eight can be arranged in pairs so that there are thirty-six possible Rhesus constitutions —

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CDE/CDE | CDe/CDe | CdE/CdE | Cde/Cde | cDE/cDE | cDe/cDe | cdE/cdE | cde/cde |
| CDE/CDe | CDe/CdE | CdE/Cde | Cde/cDE | cDE/cDe | cDe/cdE | cdE/cde | |
| CDE/CdE | CDe/Cde | CdE/cDE | Cde/cDe | cDE/cdE | cDe/cde | | |
| CDE/Cde | CDe/cDE | CdE/cDe | Cde/cdE | DE/cde | | | |
| CDE/cDE | CDe/cDe | CdE/cdE | Cde/cd | | | | |
| CDE/cDe | CDe/cdE | CdE/cde | | | | | |
| CDE/cdE | CDe/cde | | | | | | |
| CDE/cde | | | | | | | |

There are six antibodies anti-C, anti-c, anti-D anti-d (not yet encountered), anti E and anti-e. If an individual is $\frac{C}{C}$ his erythrocytes will react with anti-C but not with anti-c if he is $\frac{c}{c}$ they will react with anti-c but not with anti-C, whilst if he is $\frac{C}{c}$ they will react with both anti-C and anti-c. The same is true in the case of the D and d E and e antigens and the anti-D anti-d anti E and anti-e antibodies. So that there are twenty-seven possible ways in which a given sample of erythrocytes can react with the six antibodies.

| | *Genotype* | *anti-C* | *anti-c* | *anti-D* | *anti-d* | *anti-E* | *anti-e* |
|---|---|---|---|---|---|---|---|
| 1 | CDE/CDE | + | − | + | − | + | − |
| 2 | CDE/CDe | + | − | + | − | + | + |
| 3 | CDE/CdE | + | − | + | + | + | − |
| 4 | CDE/Cde | + | − | + | + | + | + |
| 5 | CDE/cDE | + | + | + | − | + | − |
| 6 | CDE/cDe | + | + | + | − | + | + |
| 7 | CDE/cdE | + | + | + | + | + | − |
| 8 | CDE/cde | + | + | + | + | + | + |
| 9 | CDe/CDe | + | − | + | − | − | + |
| 10 | CDe/CdE | + | − | + | + | + | + |
| | CDe/Cde | + | − | + | + | − | + |
| 12 | CDe/cDE | + | + | + | − | + | + |
| 13 | CDe/cDe | + | + | + | − | − | + |
| 14 | CDe/cdE | + | + | + | + | + | + |
| 15 | CDe/cde | + | + | + | + | − | + |
| 16 | CdE/CdE | + | − | − | + | + | − |
| 17 | CdE/Cde | + | − | − | + | + | + |
| 18 | CdE/cDE | + | + | + | + | + | − |
| 19 | CdE/cDe | + | + | + | + | + | + |
| 20 | CdE/cdE | + | + | − | + | + | − |
| | CdE/cde | + | + | − | + | + | + |
| 22 | Cde/Cde | + | − | − | + | − | + |
| 23 | Cde/cDE | + | + | + | + | + | + |
| 24 | Cde/cDe | + | + | + | + | − | + |

| | Genotype | anti-C | anti-c | anti-D | anti-d | anti-E | anti-e |
|---|---|---|---|---|---|---|---|
| 25 | $\frac{Cde}{cdE}$ | + | + | − | + | + | + |
| 26. | $\frac{Cde}{cde}$ | + | + | − | + | − | + |
| 27 | $\frac{cDE}{cDE}$ | − | + | + | − | + | − |
| 28. | $\frac{cDE}{cDe}$ | − | + | + | − | + | + |
| 29. | $\frac{cDE}{cdE}$ | − | + | + | + | + | − |
| 30. | $\frac{cDE}{cde}$ | − | + | + | + | + | + |
| 31 | $\frac{cDe}{cDe}$ | − | + | + | − | − | + |
| 32. | $\frac{cDe}{cdE}$ | − | + | + | + | + | + |
| 33 | $\frac{cDe}{cde}$ | − | + | + | + | − | + |
| 34. | $\frac{cdE}{cdE}$ | − | + | − | + | + | − |
| 35. | $\frac{cdE}{cde}$ | − | + | − | + | + | + |
| 36. | $\frac{cde}{cde}$ | − | + | − | + | − | + |

Since the genotypes

| | | | | |
|---|---|---|---|---|
| $\frac{CDE}{cdE}$ (7) | and | $\frac{CdE}{DE}$ (8) | a reduction by | |
| $\frac{CDe}{cde}$ (5) | | $\frac{Cde}{De}$ (24) | | 1 |
| $\frac{CDE}{De}$ (6) | " | $\frac{CDe}{cDE}$ ( ) | " | |
| $\frac{CdE}{cd}$ (21) | | $\frac{Cde}{cdE}$ (5) | | 1 |
| $\frac{CDE}{Cde}$ (4) | " | $\frac{CdE}{CDe}$ ( ) | | 1 |
| $\frac{DE}{cde}$ (30) | " | $\frac{cDe}{cdE}$ (3) | " | 1 |
| $\frac{CDE}{cde}$ (8), $\frac{CDe}{cdE}$ (14), $\frac{CdE}{De}$ (9) | | $\frac{cDE}{Cde}$ (3) | " " | 3 |
| | | | | 9 |

are identical in respect of gene content the thirty-six genetic constitutions in the above list are reduced to twenty-seven. The commonest constitutions in our population are

$$\frac{CDe}{cde}\,(15)\quad \frac{CDe}{CDe}\,(9)\quad \frac{cde}{cde}\,(36)\quad \frac{CDe}{cDE}\,(12),\quad \frac{cDE}{cde}\,(30)$$

in this order Together they account for about 87 per cent. of all individuals

Another gene has recently been identified $C^w$ It is a rare allele of C and c, the three forming a multiple allelomorphic series The erythrocytes of an individual carrying this gene

$$\left(\frac{C^w}{C^w},\quad \frac{C}{C^w}\quad \frac{c}{C^w}\right)$$

possess an antigen $C^w$ which reacts with the anti $C^w$ antibody *containing serum.*

ERYTHROBLASTOSIS FŒTALIS

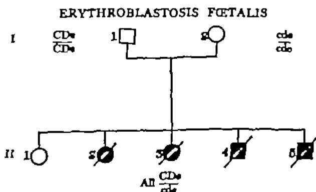



FIG. 4.—Pedigree showing the mode of inheritance of the Rhesus antigens

All ova contain the gene group cde and all spermatozoa the gene group CDe. All the offspring will therefore have the constitution $\frac{CDe}{cde}$ their erythrocytes will react with antibodies anti C anti-c, anti D anti-d and anti-e. The only serum which will give a negative reaction is anti-E. The mother has no antigen D and so is capable of producing antibody anti D in her serum. The father transmits the gene D and therefore the antigen D to all his offspring and

so if the mother produces antibody anti D this will react with the erythrocytes of her children. It will be noted that the production in the mother's serum of antibody anti D is slow so that the first born is not affected. It will also have been noted that the mother has no antigen C and so is capable of producing antibody anti-C as well as anti D How is it then that it is the latter that does the damage? For the present all that can be said is that of the two the latter is the stronger

ERYTHROBLASTOSIS FŒTALIS

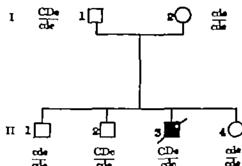



FIG. 5.—Pedigree showing the mode of inheritance of the Rhesus antigens

The father $I_1$ is heterozygous for D he elaborates two forms of spermatozoa, CDe and cde, in equal numbers The offspring can therefore be either $\frac{CDe}{cde}$ or $\frac{cde}{cde}$ The mother can be sensitised by the $\frac{CDe}{cde}$ child. Any subsequent child can be either $\frac{CDe}{cde}$ or $\frac{cde}{cde}$ If $\frac{cde}{cde}$ the anti D antibody elaborated in the mother's serum in response to the D antigen in the first child's erythrocytes will leave the subsequent child unharmed but if the child should be $\frac{CDe}{cde}$ then the mother's anti-D antibody can attack the child's D antigen and so cause erythroblastosis fœtalis.

The medicolegal determination of the Parent—Progeny relationship by reference to the ABO MN R S and P antigenic constitutions of parents and child respectively is of

course, the presentation of purely genetical evidence. This can be reinforced by other information relating to other genetical differences between putative parents and the child, differences in respect of such abnormal characters as have been used in this book to illustrate the various modes of inheritance or in respect of normal characters such as, for example the ability to appreciate the bitter taste of phenyl-thio-urea in dilutions as low as one in a million. This ability is based on an autosomal dominant gene T (for taster) unaffected in its action by environmental factors. Tasters may therefore be homo- or heterozygous Seventy per cent. of the population are tasters If the mother and the putative father are non-tasters and the child is a taster then the man in the case is not the father (Phenyl thio-urea is also known as Phenyl thio-carbomide P T C )



## CHAPTER V

### COMPLICATIONS

It has been stated that the action of a gene is influenced by that of the other genes in the genotype as well as by environmental agencies so that one and the same gene it would appear does not always yield the same end result It is the teaching of genetics that the gene itself does not vary save only through mutation, and that variations in respect of its effects are caused through the interference with its action by other genes in the genotype or by environmental agencies It is desirable at this point to consider the nature and the extent of such variability

The genes which have been used to demonstrate the principles of Mendelian inheritance have been such as in their action were not affected to any considerable extent by other genes or by forces of the environment They were selected for this very reason. It is legitimate as well as sensible to begin an account of this kind with relative simplicities and then proceed to complexities. It has to be recognised that the birth of the science of genetics might have been postponed for a very long time had it not happened that Mendel chanced to choose as his experimental material a plant with seven pairs of contrasted characters showing no linkage, one of each pair being a complete dominant, the other a recessive and none of *them in their development affected to any discernible degree* by any influence other than that of the one responsible gene. Had Mendel chosen not *Pisum sativum* but *Zea mays* (maize) for example he would have obtained an $F_1$ with a phenotype that was intermediate between the two parental ones and the absence of dominance might have hidden the clues to genetic purity segregation and independent assortment.

It is not difficult to fit such intermediacy as was seen in the cases of the A and B and of the M and N blood group characters into a general scheme *if it is encountered after* an understanding of the Mendelian laws has been secured. Having considered instances in which gene action has been

uncomplicated by any other influence it is now possible hopefully to examine cases in which the character based upon a particular gene is subject to variation in expression.

## Incomplete Dominance

The non-red hair colours are dominant to the red The alleles responsible are autosomal. The heterozygote can often be recognised by a reddish tinge to the hair and by heavy freckling Brown eye colour is dominant to blue but in many instances the eye colour of the heterozygote would seem to be a mixture of brown and blue. It is known that all eyes are blue and that a brown eye is one in which in front of the layer of blue pigment a layer of brown pigment is deposited as development proceeds. It may well be that a difference in the dosage of the dominant gene, one or two makes a difference to the time of or in the rate of the deposition of this brown pigment. Examples of a difference in the phenotypes based on the double and on the single dose respectively of a dominant gene are plentiful in forms other than man and are, of course responsible for the 1 2 1 ratio in place of the 3 1 among the progeny of the mating of two (monogenic) heterozygotes.

The heterozygote who carries the recessive gene for the Laurence Moon Biedl syndrome is often not completely without certain of the stigmata of the disease, obesity for example, the heterozygote carrying the recessive gene for xeroderma pigmentosum is often freckled These observations support the contention that dominance and recessiveness are never complete. It is convenient however for purposes of discussion to pretend that they are.

## Modifying Genes

Albinism has been presented as a character based on an autosomal recessive gene. The albino is therefore necessarily a homozygote. But the hair is not white the eyes pink and the general build and vigour subnormal in all cases. Sometimes an albino has light yellow hair and pale blue eyes and is unexceptional in respect of vigour and body build.

The most reasonable explanation of some of this variation is that it is the result of the action of modifying genes. As has already been stated the notion of the "unit character"

due to the action of a single gene in the simplex or duplex state has been discarded It is now accepted that in the fashioning of a given character very many if not all of the genes in the genotype play a part. One gene is the principal agent, the rest play a secondary role. Most genes exert a pleiotropic action. But these are not the modifying genes. A modifying gene, according to the commonly accepted definition, is one that, acting alone, yields no phenotypically detectable result, but when associated with others affects their action in a definite and constant way exaggerating or suppressing this it modifies the action of the gene or genes involved in the production of a given character

Friedreich's ataxia is a rare monogenic autosomal recessive character There is a progressive degeneration of the nervous system resulting in loss of power in the legs, trunk, arms and head Its onset is usually in early adult life so that the reproductivity of affected individuals is considerably diminished. Modifying genes have been identified which affect the manifestation of this character

The albino gene can find itself incorporated in a variety of genotypes some containing genes which modify its action, others not including such genes. In the second the albino genes will find complete expression, in the first their action can remain incomplete. So also in the case of a dominant gene. Modifiers can yield incomplete dominance, especially in the heterozygote, and so lead to intermediacy in characterisation. If this is so then it is to be expected that the homozygote will show less variability in the expression of a character than will the heterozygote. The more variable a character is in its expression the more probable will it be that the gene for it is present in the simplex state.

The interrelation of gene and gene is not always that of principal and modifier of course. Piebalding is caused by a dominant autosomal gene, but manifestly it can act only in a genotype which includes genes that yield a darkly pigmented skin. The piebalding and albinism genes in co-operation could not possibly produce a piebald albino.

That a modifying gene is not the creation of the needs of a harassed geneticist can easily be proven by an appeal to appropriate matings. Principal gene and modifier can be disjoined dissociated as can also the dominant and recessive

allele and then it can be seen that though characters in their expression are subject to much variation yet the genes are stable, discrete and specific in their various actions and are in no way themselves affected through their association with other genes or by environmental influences (save, of course that certain environmental agencies can and do speed up their mutation rate)

## Variations in Respect of the Degree of the Expression of a Character and of the Penetrance of a Gene

The degree to which the effects of a gene are variable is the measure of the *expression* of the character in question. Epiloia with its neuroglial nodules in the brain its mental deficiency its adenoma sebaceum on the face and along the nasolabial folds is based on an autosomal dominant gene. But not all sufferers from this condition present all these abnormalities—that is to say the complete syndrome is not always exhibited The degree of the expression of this character varies greatly in different cases. Brachydactyly and phalangeal synostosis autosomal dominants, are invariably displayed by the individuals who possess the corresponding gene but the degree of the abnormality varies widely in degree in different individuals, ranging from near normality to gross abnormality Nevertheless whatever may be the degree of this expression the character however incomplete and imperfect can be recognised

A gene can be known to be present in a given genotype and yet in the phenotype there can be no hint of it. Polydactyly based on a dominant autosomal gene, is very variable in expression, in some instances there is no discernible manifestation of the character though it is known that the gene is present in the genotype of the individual Diabetes mellitus an endocrine disturbance of carbohydrate metabolism taking the form of an insufficiency of production of insulin by the cells of Langerhans of the pancreas is in certain instances a genetic character based on an autosomal dominant gene. But in only about 10 per cent of individuals possessing the gene is the character displayed The frequency with which a gene produces any effect at all is the measure of its *penetrance* The

penetrance of the gene for diabetes mellitus is thus 10 per cent. Possibly environmental agencies determine who among the possessors of this gene shall exhibit the character

Diabetes insipidus due to an abnormality in the functioning of the posterior lobe of the pituitary and characterised by an intense thirst and polyuria, is in certain cases the expression of an autosomal dominant gene present in the heterozygous state and with a low penetrance.

DIABETES INSIPIDUS

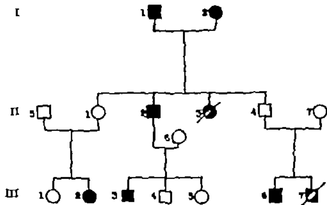



Fig. 16.—Pedigree of diabetes insipidus, showing the effects of low penetrance on the part of the gene $II_1$, and II must have possessed the gene since they produced affected offspring yet they themselves did not exhibit the character

Manifestly if individuals do not disclose the presence of a dominant gene within their genotypes by the display of the corresponding character the interpretation of a family pedigree can present considerable difficulty and confusion. There can be skipping of generations, affected individuals can have unaffected parents and meaningless ratios of affected and unaffected can be obtained Far more than one pedigree will be required for the recognition of the true genetic nature of the condition

It will be appreciated that it is not always a simple matter to distinguish between a dominant gene with a low penetrance and a recessive. The existence of consanguinity in the parents can help towards a decision since a recessive tends to appear in several members of an inbred stock whilst a dominant for its expression depends not at all on consanguinity

In the case of totally sex-linked X borne recessive genes it appears that in general the degree of the expression of the character in the male possessing but one gene is equal to that in the female possessing two whilst in the heterozygous female there is variability Instances are on record in which such a female has displayed the recessive character though not to the full. For example, some 3 per cent of females heterozygous for the gene for red-green colour blindness are affected So also in the case of hereditary nystagmus This recessive gains expression in some 30 per cent. of females heterozygous for it. The degree of the expression of the character does not vary but the penetrance of the gene does in so far as the heterozygous female is concerned.

A considerable number of fairly common pathological conditions have been recorded as being of genetic origin, being based on dominant genes having a very low penetrance. These include leukæmia pernicious anæmia, Graves disease, gastric ulcer asthma, paroxysmal tachycardia eunuchoridism, inguinal hernia and congenital dislocation of the hip When dealing with a condition such as leukæmia which has a penetrance of around 1 per cent. it must remain difficult to persuade oneself let alone anyone else, that the condition is in fact genetically caused It is because in the case of so many diseased conditions there is a wide range of expression and much variation in respect of penetrance that it is undesirable to include in a manual of this kind long lists of diseases that have been recorded as being the expression of genic action. To do so would be to mislead the clinician. The fact is that in the present state of our knowledge the interpretation of the majority of human pedigrees demands an experience and an acquired skill that are possessed by few As things are there is a great deal that is of considerable genetical value lost because there is no easy mechanism whereby pedigrees constructed by individual practitioners and apparently meaningless in themselves can be submitted to some central bureau where they could be examined against the background of accumulated knowledge It is most unlikely that any one practitioner would ever be able to recognise a genetic causation in single instances of low penetrance and variable expression.

The difficulties presented by a family history do not all derive from differences in character expression and in genic

penetrance. Quite commonly they result directly from faulty recording. To obtain full and accurate information concerning the illnesses and abnormalities of three generations of a family is an impossibility in the great majority of instances. Little or more commonly nothing is known by the propositus of the affairs of the grand-parental group. Uncles, aunts and cousins have passed out of ken, have migrated or died. Nothing is recorded in the family bible of the individuals who died in infancy save that they did so die. So it is that a pedigree commonly has to be built by the physician largely out of anecdote, which is never a satisfactory foundation on which to erect a scientific diagnosis. What are needed more than anything else for the speedy advancement of our knowledge of human genetics in its relation to clinical medicine are (1) the country-wide systematic preparation of pedigrees by genetically informed and interested medical practitioners and (2) a storehouse where these can be received, pooled and interpreted.

## Differences in the Time of the Display of a Character

Yet another complication is provided by the fact that different genes produce their effects at different points in the life history of the individual. The example usually cited is that of Huntington's chorea, the condition in which degenerative changes in the cerebral cortex and *corpus striatum* are responsible for involuntary and inco-ordinated muscular movements associated with progressive mental deterioration. The disease is caused by the action of a dominant autosomal gene which affects not the processes of development but those of degeneration. The average age at which its effects are to be discerned is around thirty-five so that it is possible for many an affected individual whilst still normal phenotypically to marry and produce a family. The sufferer is usually a heterozygote so that, married to a normal woman, he can be expected to produce normal and affected in equal numbers. The heterozygous affecteds in their turn, disregarding their father's fate, will marry and reproduce before they themselves succumb. The features of a pedigree showing this condition will therefore be determined by the age distribution among the individuals comprising it.

## Multifactor Inheritance

There is the possibility that certain abnormal characterisations are themselves *multifactor* in nature, that is to say are based upon a number of genes each of which makes a small contribution to the end result these contributions being additive so that different combinations of these genes yield different grades in the expression of the character Such variability would have to be distinguished from variations in the expression of a unit character It certainly is the case that some normal characters have such a multifactor basis. Stature skin colour and thickness intelligence and disease resistance would seem to be examples of this multi factor inheritance The proper methods for the study of such characters are mainly biometrical, biometry being the science of the measurement of living things. It is outside the scope of this book to present and to discuss these methods It must suffice to give a hypothetical illustration of the manner in which many genes acting together can yield a series of end results differing one from the other quantitatively

It is known that several genes are responsible for the differences in skin colour which distinguish negro from white. In a group including whites blacks and their hybrid offspring from various matings it is possible to arrange the members in a sequence ranging from black to white through mulatto quadroon octoroon and so on Each grade differs from all the rest in respect of a difference in the amount of melanin (and also of a yellow lipochrome)

If it is assumed that these differences rest on two gene pairs Aa and Bb without dominance and if the four genes have a different pigment producing power A = 6 B = 4 a = 3 b = 2 it can be seen that segregation among the offspring of two AaBb individuals can provide a whole range of colour types.

negro AABB × aabb white
6644 3322
20
AaBb uniformity of the $F_1$
6342
5

| AABB | AABb | AaBB | AAbb | AaBb | aaBB | Aabb | aaBb | aabb | |
|---|---|---|---|---|---|---|---|---|---|
| 20 | 18 | 17 | 6 | 5 | 14 | 3 | | | |
| 1 | 2 | 2 | | 4 | | | | | Frequency |

Bodily stature, disregarding the pathological giant and the dwarf is the end result of the interplay between genetic capacity and environmental encouragement. It has been established that about 90 per cent. of the variability in respect of stature in a people like ourselves is to be ascribed to genetic causes The fact that with improved nutrition and general sanitation the average height of the people has increased that the present generation has an average height which exceeds that of its predecessor does not disturb this statement. Several genes are concerned, each alone producing a small effect. Dominance would appear to be involved since there is a tendency for shortness to be dominant to tallness. It is to be observed that tall parents, medium and short parents produce tall medium and short offspring but that talls have more talls than do mediums and shorts On the average, therefore if the offspring of a large number of parents of the tall and short classes are measured it will be found that the offspring of tall parents are not so tall as were the parents, though taller than the offspring of the mediums and shorts and that the offspring of short parents are on the average taller than were their parents—the phenomenon known as regression to the mean, a direct consequence of the operation of the laws of chance

## Mental Disorders

Examples of mental diseases which are the direct expression of genetic action uninfluenced or only slightly influenced by environmental forces have been considered. Huntington's chorea is based on an utosomal dominant gene, amaurotic family idiocy on an autosomal recessive. This latter disease is found more frequently in Jewish families than in others. The child, apparently quite normal at birth, begins around three to six months of age to exhibit a progressive mental impairment which ends in idiocy There is also a progressive paralysis of the body as a whole, whilst visual cuity progressively diminishes to end in blindness. The average age at death is eighteen months, all sufferers being eliminated before the end of the third year of life. There are pathognomonic retinal changes taking the form of a large cherry-red spot in the region of the macula whilst the cells of the whole of the nervous system in their degeneration become distended with abnormal lipoid material.

## Multifactor Inheritance

There is the possibility that certain abnormal characterisations are themselves *multifactor* in nature that is to say are based upon a number of genes each of which makes a small contribution to the end result, these contributions being additive so that different combinations of these genes yield different grades in the expression of the character Such variability would have to be distinguished from variations in the expression of a unit character It certainly is the case that some normal characters have such a multifactor basis Stature skin colour and thickness intelligence and disease resistance would seem to be examples of this multifactor inheritance The proper methods for the study of such characters are mainly biometrical biometry being the science of the measurement of living things It is outside the scope of this book to present and to discuss these methods It must suffice to give a hypothetical illustration of the manner in which many genes acting together can yield a series of end results differing one from the other quantitatively

It is known that several genes are responsible for the differences in skin colour which distinguish negro from white In a group including whites blacks and their hybrid offspring from various matings it is possible to arrange the members in a sequence ranging from black to white through mulatto quadroon octoroon and so on Each grade differs from all the rest in respect of a difference in the amount of melanin (and also of a yellow lipochrome).

If it is assumed that these differences rest on two gene pairs Aa and Bb without dominance, and if the four genes have a different pigment producing power A = 6 B = 4 a = 3 b = 2 it can be seen that segregation among the offspring of two AaBb individuals can provide a whole range of colour types.

negro AABB × aabb white
6644 3322
20 1

AaBb uniformity of the $F_1$
6342
15

| AABB | AABb | AaBB | AAbb | AaBb | aaBB | Aabb | aaBb | aabb | |
|---|---|---|---|---|---|---|---|---|---|
| 20 | 18 | 17 | 16 | 15 | 14 | 13 | 1 | | |
| 1 | 2 | 2 | | 4 | 1 | 2 | | 1 | Frequency |

In instances in which both genetic and environmental factors are concerned in aetiology the twin method of investigation is of particular usefulness It was Galton, as long ago as 1883 who first called attention to the fact that the biology of monozygotic as contrasted with that of dizygotic twins affords a means of distinguishing between the effects of Nature and of Nurture respectively Monozygotic twins share a common genotype dizygotic twins are no more genetically similar than are brothers and sisters born at different times. The quotation concerning schizophrenia on page 4 refers to a careful and critical evaluation of the nature—nurture problem on the basis of a clear mono- and di-zygosity Out of a consideration of these and similar findings it is possible to reach the following conclusions Genetic factors are not always involved in the aetiology of the schizophrenic psychoses but as a general rule they play an important part. By themselves they do not suffice to produce the condition and in their action they are not highly specific.

For the present we do not know what the environmental agents are which play a part in the production of schizophrenia. This in itself is a sufficient explanation of our lack of knowledge of the genetic factors that are concerned All that can be said is that the relatively high incidence of the condition amongst sibs of affected individuals, the unusual frequency of consanguinous marriages among the parents and the differences in the incidence among mono- as contrasted with di zygotic twins most strongly suggest that a recessive gene or genes underlies the condition that the expressivity of this gene is variable and that certain as yet undefined environmental circumstances are required if the expression of the character is to be at all complete.

The findings concerning manic-depressive psychosis are very similar and the same explanation has to be offered. The genetic component would seem to be an autosomal dominant, the dominance being incomplete in many instances. The environmental agencies concerned are as yet unidentified.

## MENTAL DEFICIENCY

This condition has already been encountered in the description of epiloia. Phenylketonuria (oligophrenia phenylpyrouvica) is the condition in which the individual excretes

phenylpyruvic acid (a derivative of the amino-acid phenyl alanine) in the urine and which is encountered among low grade mental defectives. An autosomal recessive gene is responsible not only for the metabolic abnormality but also for the associated mental defect. This variety of mental defect can therefore be identified by an analysis of the urine. These two conditions account for about 1 per cent. of the whole. But there is a mental deficiency which is not an ingredient of a syndrome in a human population there are individuals who are to be distinguished from their fellows by reference to the relatively low grade of their general intelligence as measured by means of suitable tests It is commonly accepted that this quality is determined by genetic factors to the extent of some 50-75 per cent. By appropriate psychometric tests the mental age of an individual can be ascertained

$$\text{I.Q (intelligence quotient)} = \frac{\text{Mental age}}{\text{Actual age}} \times \frac{100}{1}$$

If a representative sample of the population is so measured it is found that the variation among them ranges between two extremes The whole range is broken down arbitrarily into a number of categories Those with an I Q of less than 20 are classified as idiots those with an I Q between 20 and 50 as imbeciles and those with an I Q between 50 and 70 as feeble-minded or mentally defected (50-55 low-grade, 55-62 mid-grade 62 70 high-grade moron). These grade imperceptibly into normality as judged by these standards. An I Q of 70-80 = borderline 80-90 = dull 90-110 = normal 110-120 = superior 120-140 = very superior 140 and over = genius. No one can say where exactly stupidity ends and feeble-mindedness begins or when feeble-mindedness becomes imbecility

Mental deficiency is divided into primary and secondary The primary—the genetic group—is said to constitute some three quarters of the whole. In certain pedigrees a single autosomal recessive gene would seem to be responsible. Among the sibs of defectives about one fifth are likewise defective when both parents are phenotypically normal and nearly all are defective when both parents are defective.

The environmental causes of mental deficiency are intra uterine (Mongoloid idiocy) birth injury hydrocephalus,

cerebral syphilis, meningo-encephalitis hypothyroidism and certain congenital malformations of the cerebral tissue and cranium (microgyria, porencephaly and syncephaly).

It has been suggested that general intelligence is a graded character multifactor in origin It is reasonable therefore to regard the high-grade mentally deficient as being those who are poorly endowed in respect of these genes. They are at the one end of the scale at the other end is the exceptionally intelligent individual. The difference between the two is like the difference between the best and the worst hands in a game of bridge. There is nothing the matter with the cards but everything wrong with the hand that the dealer has delivered. But it is probable that, as the scale is descended towards the imbecile and idiot categories, low-grade mental deficiency when genetic in origin is caused by specific genes by genes that do not belong to the constellation of genes in the multifactor series In other words the greater divergence from the mean of intelligence the more probable it is that the cause is a specific gene When the cause is not genetic it is an environmental agency of considerable potency provoking a large reaction.

It will not have escaped notice that the geneticist considering the problems of heredity and disease depends entirely on the clinician for the definition of the character the mode of inheritance of which he is studying There is no difficulty when the character is an anatomical detail that is easy of recognition and unchanging in expression. Ptosis is always ptosis. Similarly diabetes insipidus or amaurotic family idiocy are labels that cannot be differently used by different clinicians. But when different labels are given by different authorities to one and the same condition or when one and th same label is used by different authorities to identify different conditions the geneticist s task becomes hopeless Mental deficiency for the most part is a grade of an attribute rather than an attribute itself it is a section of the curve which depicts the range of intelligence in a population Within the group of mental defectives there is again a graded variety from high to low Thus even if environmental agencies in aetiology are disregarded to trace its inheritance and to identify its genetical basis still remains difficult.

Furthermore whilst the official definition of mental

deficiency is a condition of arrested or incomplete development of the mind before the age of eighteen, much more than the intellectual function can be impaired the emotional and conative functions also have to be considered and these are not to be measured by the tests which yield the I Q

In the case of that mental deficiency which results from a genotype poorest in respect of the genes for general intelligence and which therefore is the one extreme of the range that extends from dull to brilliant, it can be seen that if like tends to marry like their offspring will, judged as a group tend to be nearer the mean than were their parents The most intelligent individuals of one generation will possess the same equipment as the cleverest of the succeeding generation and the dullest of one generation will be as dull as the dullest of the next, but brilliance will not beget only brilliance and dullness only dullness. The shuffling and dealing of the multiple factors underlying general intelligence will result in the production by the brilliant of the quite ordinary and of brilliance by the ordinary and the dull. Only two individuals each completely homozygous for all the genes concerned and therefore identical in respect of them could yield offspring all equal to their parents, and then only if environmental factors counted for nothing in so far as this character is concerned. Nevertheless the mating of well above the mean by well above the mean will yield offspring who on the average will be above the mean whilst the mating of well below the mean by well below the mean will yield offspring who on the average, will be below the mean. The question thus arises which group is producing most offspring

Evidence has been presented which strongly suggests that there is in fact a negative correlation between the intelligence of a child (as measured by the present-day tests) and the size of the family to which the child belongs. The explanation of this rather frightening fact would seem to be that the more intelligent people marry later and produce fewer children. Manifestly the evidence must be examined with the greatest care for it is indeed difficult to disentangle that part of an individual's intelligence that is the expression of his genotype from that which pertains to his social inheritance—education, home and opportunity If the lower intelligence of the members of large families is a genetic phenomenon then

only a differential birthrate in the opposite direction—the more intelligent producing more offspring—could avoid the steady decline in the intelligence of the population as a whole. If the lower intelligence of the members of large families is an environmental effect then social amelioration would eliminate the difference. Undoubtedly both genetic and environmental causes are operating but at present it is impossible to contrast them at all accurately in respect of their relative importance It is useless to compare the members of large families of one socio-economic group with the members of small families of another Differences in the uterine environment seem to affect the I Q since this varies with the birthrank. The later members of a large family tend to have an older mother than do the members of a small family and the I Q of a child seems to be influenced by the age of the mother On the whole the I Q of city children is higher than that of the country children.

The different socio-economic classes tend to show different levels of intelligence as measured by the standard tests the higher the class the higher the I Q The children of a group of parents with a high I Q tend to have a higher I Q than that of the children of a group of parents with a low I Q

| *Socio-economic group of parents* | *Average I Q of children* |
|---|---|
| Unskilled labourers | 96·0 |
| Partially skilled | 98·0 |
| Semi-skilled | 05· |
| Skilled | 07·5 |
| Semi-professional and managerial | 15·0 |
| Professional | 16·0 |

When children are reared in institutions apart from their parents there tends to be a correlation between their I Q and that of their parents. According to other investigations the I Q.s of foster children accord more closely with those of their foster parents than with those of their actual parents. The I Q.s of children transferred from bad environment to good have, in certain studies moved up six points. The I Q.s of identical twins often differ though as a rule not markedly (reared together 5·9 reared apart 7·7 exceptionally by as many as fifteen points) but usually they are much nearer than are those of fraternal twins (8·4) and very much nearer than those of brothers and sisters born t different

times (15). Malnutrition does not seem to affect basic intelligence The removal of tonsils and adenoids does not influence the I Q Deafness and eye defects must necessarily affect the performance of a child in so far as many of these tests are concerned There is no sex difference in respect of I Q scores. In America Chinese and Japanese children score just as highly as do American and European children judged as groups The children of Jewish immigrants judged as a group secure the highest scores Negro children have a lower average than do white children but the children of northern negroes score some seven points higher than do those of southern negroes. In 1917 18 when exposed to the American Army Alpha test, negro recruits from the cities of the north obtained a higher median score than did white recruits from certain of the rural areas of the south

These and a dozen other complications make it difficult to recognise the role of the gene in the progressive decline of the intelligence of the population as a whole which, in the considered opinion of certain students of the matter would seem to be taking place It is of the utmost importance that *we should know whether or not this is so. If general intelligence* can be compared with stature both being the product of the interplay of nature and nurture and if as is the case, the average height of the population has increased as the result of improved sanitation, it would be expected that with improvements in education the average intelligence of the people would also have risen If it is declining then in its establishment the initial genetic endowment must be the more important agent. Medicine cannot be mistaken in supporting all measures that tend to improve the environment that is the uterus the home and the school. Of particular medical interest are the maternal conditions that are associated with congenital defects and derangements since it is reasonable to entertain the view that the causes of these, operating to a less extent could lead to damage which, though not expressed as a recognisable anatomical abnormality could yield a lowered I Q Further more medicine could not be wrong in presenting the view that the more *intelligent among the population should* in the interests of our stock, reproduce sufficiently to ensure that they are adequately represented in the next generation But it must not be forgotten however that in our kind of society

there is plentiful room for the dull and backward, even for the high and middle grade moron. We provide appropriate environments and tasks for them.

## CONSTITUTION DIATHESIS

So far the discussion has concerned itself with characters that were referable to particular genes—the gene for syndactyly and so on—or with characters that were based upon the interaction of several genes—multifactor inheritance, the genes for stature, for disease resistance of a general kind for intelligence of a general kind and so on. But there are attributes which would seem to be referable not to a particular gene or group of genes but which are the reflections of the genotype as a whole, of the genetic make up of the individual of the individual constitution. To suggest that this is so is not to stretch genetical argument beyond reasonable limits surely It is merely to say that whereas in multifactor inheritance the genes concerned can be identified by appropriately planned investigation there are other traits characters undoubtedly genetic and certainly referable to the interaction of very many genes whose exact genetic basis is as yet hidden from us For the present therefore we must be content to present the view that they are genetic and are trustworthy indications of significant differences between the genotypes of different individuals, types, ethnic groups

Rheumatism in childhood with its joint pains fever and endocarditis affects about 2 per cent. of the population at risk and is responsible for some 80 per cent. of all deaths from heart disease of persons under forty years of age It is the cause also of a very great deal of invalidism. In the present state of our ignorance it was inevitable that a genetic cause should be sought It has been suggested that a recessive gene lies at the root of a susceptibility or diathesis and that this gene (in the duplex state) demands for its expression a certain constellation of environmental conditions. It is indeed difficult to accept such a suggestion. It must remain exceedingly difficult to demonstrate the role of the gene in the causation of this condition until nature and importance of such environmental factors as poverty and climate have been defined.

Evidence of a definite familial incidence of exophthalmic

goitre has been presented affected sibs occur far more frequently than do affected parents or children It has been suggested that an autosomal recessive gene is concerned and mental shock, infection and other non-genetic agencies provoke the expression of the character in such as possess the gene in the duplex state.

If there is a tuberculous diathesis what does this mean genetically? It would seem that every individual can become tuberculous but not always with the same ease. Some are more prone than others some more resistant. Most authorities are of the opinion that such differences are due to an acquired immunity but it is undoubtedly the case that different genotypes in virtue of the genes they include, equip their possessors with different characterisations and that certain genotypes may include genes which in their interaction yield this quality of resistance to tuberculosis. If so this resistance would be expected to be of a graded kind, the grade being determined by the actual genotype.

The evidence that genotypic differences are responsible for differences in resistance and susceptibility must be regarded as inconclusive. The same is true of the role of the gene in the ætiology of cancer in the human subject. Genes and genotypes are involved, it would seem, but to what extent and in what way are not yet known

## Different Genes and Genetic and Environmental Factors Yielding the Same Character

Then there is the difficulty that arises from the fact that one and the same defect or derangement can be caused by each of a number of genes quite distinct one from the other For example epidermolysis bullosa is recognised by the clinician to exist in three forms the simple, the mild and the severe. The first two are autosomal dominants the third a partially sex linked recessive Spastic paraplegia is in certain instances a partially sex-linked recessive in others it is an *autosomal dominant*. *Retinitis pigmentosa* in different pedigrees is a partially sex linked dominant a partially sex linked recessive a totally sex-linked recessive, an autosomal dominant and an autosomal recessive the last being distinguished from the rest clinically since it adds deafness to the conditions in the eye. Of keratosis follicularis, Darrier s disease

(overgrowth of the epithelial layers of the skin, hyaline degeneration in the hair follicles especially on the head, chest, loins and extremities plus subnormal stature and mental deficiency) there appear to be two genetic forms, one an autosomal dominant and the other a totally sex-linked dominant. Atheroma and polydactyly in different instances behave as autosomal dominants and as autosomal recessives. Defective enamel of the teeth has been reported as an autosomal dominant and also as a totally sex-linked dominant.

That there should have been a certain confusion between autosomal and partially sex-linked genes is easily under standable. The impressions obtained from pooled pedigrees can be corrected by the results of the thorough study of a combination of family pedigrees studied separately and disturbances in the ratios of affected and normal males and females can indicate that what was regarded as an autosomal gene is really a partially sex-linked one.

But there surely is nothing surprising in the fact that different genes can and do yield the same abnormality in characterisation. Normality is the outcome of a number of integrated and co-ordinated developmental processes in which the various moulding influences must be of exactly the right kind, must come into play at the right time and be of the proper strength.

If the nature of the genetic stimuli becomes altered as the result of the mutation of one of perhaps quite a large number of genes, if the timing is altered or the strength, abnormality becomes the end result. But to the varieties of abnormality that can result from interference of this nature there must be a limit. If two quite different genes should render a particular step in the development of a character abnormal and abnormal in the same kind of way affecting the timing of the entrance of a particular stimulus for example it is not surprising that in the end they yield the same character The clinician of all people, cannot be surprised that different agencies of the same general kind can evoke the same reaction nor can he be puzzled when he learns that an accident of development or an environmental force coming into play at a critical time of development can produce an end result that is identical with a character that is in other instances purely genetic. That diabetes insipidus can be in certain cases the sequel of a

pituitary tumour in others the result of a syphilitic meningitis and in still others the expression of a dominant autosomal gene merely means that the pituitary can go wrong only in a limited number of ways in so far as its effective endocrine contribution is concerned and that one and the same reaction is evoked by a variety of agencies some genetic and others environmental.

The fact that one and the same clinical entity can be caused by both genetic and environmental factors can introduce much difficulty into the interpretation of a pedigree. Deaf mutism, for example, can be the expression of an autosomal recessive gene in the duplex state It can also be the sequel of infectious disease in early infancy Deaf mutes tend to form an isolate in the population and marriage between them is not uncommon It often happens that the offspring of two deaf mutes are all normals The explanation is that the deaf-mutism of one or both of the parents was not the genetic variety but was an acquisition

## Fresh or Recurrent Mutation

Manifestly if the propositus is the first of his line to exhibit an abnormal character a study of the pedigree will yield no information whatsoever If the character he displays is known to be due to a dominant with 100 per cent. penetrance then a gametic mutation must have occurred in the germ-tract of one or other of the parents If it is a straightforward recessive then, unless the parents share a common ancestor gametic mutation must have taken place in the maternal and paternal pedigrees some generations back and the propositus is the first homozygous recessive to appear

Recurrent mutation must occur in the case of certain genes at least, for otherwise they would disappear through time as they destroy their possessors. The severe form of hæmophilia removes the great majority of its exhibitors before they transmit the gene to progeny Of the human X-chromosome two thirds are possessed by the female part of the population one third by the male. It is rare indeed for the gene for hæmophilia in the male X to survive the male that bears it. It is even rarer for those on the Xs of the homozygous hæmophilic female to pass from one generation to the next. The only hæmophilic genes that are regularly handed on are those of

heterozygous females So that unless the gene is continually reinforced the disease would die out.

Epiloia, when fully expressed slays in infancy it is only because the expressivity of this dominant autosomal gene is so variable that it can be handed on at all. The birth of an affected child to normal parents has been recorded on several occasions and there can be no reasonable doubt that this gene too is reinforced from time to time by fresh or recurrent mutation.

If it is assumed that the proportion of individuals possessing a gene that slays, a lethal gene, among the general population remains steady throughout many generations, and if the proportion of those who carrying the gene, are eliminated by it can be assessed then it becomes possible to estimate the amount of recurrent mutation that will be required to maintain the postulated equilibrium. Exercises of this kind indicate that the average mutation rate for the human genes is similar to those which have been observed in a very wide variety of animal and plant forms. It is supposed by many geneticists that the mutation frequency has become established through a process of natural selection of genes which affect the mutation frequency itself, acting over thousands of millenia and allowing the present spontaneous frequency to be as high as can be handled by the type of selective processes that operates In the case of the human subject the rigour of selection has been lowered with the result that the spontaneous mutation rate has got out of step and is higher than is required for the maintenance of an equilibrium between mutation frequency and elimination. When an equilibrium is preserved by recurrent spontaneous mutation it follows that different genes have different mutation rates since the lethals and the genes that lower the chances of transmission through the exercises of the reproductive function will demand a more frequent reinforcement through fresh mutation than will genes that advantage rather than handicap their possessors.

As has already been stated the cause of spontaneous mutation is not yet known. It is well-known that all types of short wave radiation strongly augment this tendency on the part of genes to mutate, but in ddition to provoking point " mutation, the mutation of a particular gene these agencies cause fragmentation of the chromosomes and maldistribution of chromo-

some material. A fragment, a small section of a chromosome is lost excluded from the nucleus (deletion) a piece of a chromosome rejoins the rest of the chromosome to which it belongs but upside down (inversion) a piece of one chromosome joins the other *member of the same homologous pair* (duplication) a piece of one chromosome joins a chromosome of another homologous pair (translocation) a whole chromosome is lost to the nucleus of one daughter cell and gained by the other (heteroploidy) the whole chromosome set becomes multiplied (polyploidy) Most of these phenomena have not yet been observed in man. It can safely be assumed that they occur however The artificial induction of mutation evokes nothing that does not normally occur it merely increases the frequency of the occurrence.

It can be imagined how linkage relations can be disrupted by such events as translocation, an autosomal gene becomes a *sex-linked gene and so on It is fortunate from the geneticist's* point of view that spontaneous mutation and chromosome maldistribution are so rare. Were it otherwise the building of the edifice of genetic theory would have been a hopeless task.

Is this tendency to mutate an advantage or a disadvantage to the species? It is conventional in genetics to give to a gene a name that at first sight would seem to suggest that the gene has but one action the evocation of the one character the geneticist assigns to it—the gene for ptosis the gene for albinism and so on. This suggestion is partially shattered when the gene stands for a syndrome, for example, the autosomal recessive gene for the Laurence Moon Biedl syndrome or the autosomal dominant gene for blue sclerotics and for bone fragility The great majority of genes are pleiotropic it is merely a matter of convenience to name them according to their most obvious or most serious effect Genes interact *with one another* large numbers of them are involved more or less in the production of any given character Fortunately there is usually one that is more responsible than the rest and this is the one the geneticist picks out as the gene that corresponds to the character In doing so he does not deceive himself he knows that many others are concerned There is a whole genotype lying behind a whole characterisation, and that characterisation is in harmony with the conditions

of the individual's external world. There is harmony between genotype, phenotype and environment.

If this be so, if this be normality, then mutation must destroy it. Mutation in one locus affects the whole genotype in action. This must change more or less the phenotype and this becomes out of harmony with the external world. No wonder that most mutations yield alleles that are disadvantageous to the individual in whom they find expression. Yet without mutation how could there be change? How could the genotype come into harmony with an altered environment? Mutation is the means whereby our evolutionary development has been made possible, it being assumed that we are the ascendants and not the descendants of a far more primitive stock. The variability and adaptability of a species depend on gene and chromosome changes. Adaptability is achieved through the resolution of conflict between organism and environment. The latter is in a state of flux and its changes, fast or slow, tend to make the genotypes of bygone generations no longer fit for survival. The conflict between species and habitat can be resolved either through the extinction of the species or through reorganisation of its genotype. Manifestly what is needed for evolutionary change is infrequent mutation and the opportunity for a mutant gene to find itself in various gene companies in which it can hide itself until it becomes associated with such gene companions as will suppress its deleterious actions and encourage its beneficial ones (it, like all the rest, being pleiotropic). Obviously if a mutant gene is dominant and deleterious it cannot be hidden, it will be expressed and will wipe itself out. But if it is a recessive it can exist for many generations and in a variety of genotypes before it is expressed.

A mutant gene in the beginning is a single gene. It will therefore exist only in heterozygous individuals for a considerable number of generations. During this time it can find itself in genotypes in which other genes, modifiers, can act in concert with it. If it yields an improved phenotype then it will be to the advantage of the species that this allele shall be a dominant in relation to the gene from which it sprang. If it should yield an inferior phenotype then it will be to the advantage of the species that it shall be a recessive. The modifying action of other genes can yield this dominance and recessiveness

A survey of genetic abnormalities in man shows that many of the rare disorders are simple recessives and that such as are not have a variable expressivity they are as it were, on the way to complete recessiveness. Then there are many so-called dominants seriously disadvantageous—Huntington's chorea and epiloia, for example—which are only encountered in the heterozygous state. It is not known whether the homozygous individual would exhibit the condition to an even greater degree it is highly probable that they would. Being heterozygous these individuals show considerable variability in respect of character expression and also of gene penetrance. *Thus it is that environmental agencies can exert a selective* action upon the character and through this upon the frequency with which the gene is to be found in the population.

If the characterisation of a species is in accord with the conditions of a static environment then mutation is undesirable. If the circumstances within the environment change—and we have changed those of ours profoundly during our social evolution—then mutation is desirable but it must not be frequent otherwise the essential stability of the gene would be lost. Mutation is not purposeful but random. It produces alleles of all kinds good bad and indifferent as judged by their effects upon the vital processes of the individual. The vast majority are detrimental some are lethal they eliminate themselves and are maintained only by recurrent mutation. For every fully lethal gene there are two or three which are sublethal yielding lowered viability and efficiency The former slays the latter constitute a severe handicap A very few confer undoubted advantage immediately and the selective agencies of the environment encourage their spread among the population and the development of the attribute of dominance. Most normal genes in our genotype arose through mutation presumably and they are in the vast majority of instances dominants Others yield effects which are a mixture of advantage and disadvantage. The modifying action of other genes can suppress the latter and allow for the gradual cultivation of dominance by an allele which later through selection will replace the gene from which it sprang Multiple allelomorphic series can be regarded as the provision through mutation of a variety of alleles of different merit and demerit which are available for testing and appraisal by the selective

agencies within the genotype (modifiers) and in the external environment.

### *The Possible Remote Effects of Exposure to Radiation*

Many patients are much exposed nowadays to X-rays in diagnosis and therapeusis In industry large numbers of people are exposed to the action of physical or chemical agents known to be mutagenic. Since it is established that exposure of this kind does in forms other than man lead to mutation (gene mutation, chromosome fragmentation maldistribution) the question as to whether or not such exposure in the case of the human subject yields the same results at once arises. We do not know for the matter has not received sufficient attention But if in this respect man is like the mouse then it is indeed probable that mutation has not uncommonly been produced There is good reason for the display of anxiety

The existing evidence for an adverse effect of therapeutic pelvic radiation on the foetus is conflicting Microcephaly has been reported. This can be the expression of a recess ve gene but it is difficult indeed to suppose that the radiation of a woman known to be pregnant (and therefore of a foetus already well formed) can produce mutation in the two members of a particular pair of genes It certainly might directly disturb developmental processes already in progress

But there is no safe dose and all radiation of the gonads is genetically objectionable. The testes and ovaries must always be protected, it being remembered that the frequency of mutation is directly proportional to the total dose of irradiation received regardless of how diluted protracted, interrupted or concentrated the exposure may have been. There is no threshold dose and the effects are cumulative over an indefinite period throughout the whole of an individual s lifetime. It seems probable that a total accumulated dose of about 35r applied to gametes or about 100r applied to the gonads would cause a doubling of the natural mutation rate As most mutations tend to be recessive their effects will not be disclosed for many generations which means for hundreds of years.

## CHAPTER VI

### On the Transmutation of Knowledge into Advice

With the background now provided it should be possible for the clinician to proffer sound advice based on scientific fact and reasonable interpretation to such as seek it concerning the genetic nature of the abnormality which they themselves exhibit or which their ancestors or near relatives have displayed and which they fear may reappear among their offspring That which follows will consider the nature of such advice.

To know is one thing to advise is another To marry is not necessarily to procreate. Advice based on genetical knowledge is not concerned with the cohabitation of an adult heterosexual pair it deals with the possibility that a given mated pair may produce an abnormal child Advice derived from a knowledge of genetics alone must remain incomplete it must be based also upon a knowledge of the personalities of the partners and of their socio-economic circumstances It is the offering of an understanding sympathetic, wise friend and not the overpowering instruction of an authority It is for the recipients to make decisions, it is for the adviser to aid them to ensure that their decisions are wise.

The clinician, though dealing with the problem of a particular couple is in fact playing his small but important part in shaping the future. He is influencing in small measure the frequency of a gene in the genetical constitution of a people. The family doctor is often the physician of the future

To offer advice of a general kind is of no great value. Every case must be dealt with on its own merits There are certain broad principles that can be stated however which can form the nucleus of a more detailed consideration

*An autosomal recessive* corresponding to a pathological character (and the partially sex linked recessive). It is impossible to eliminate such a gene from a population merely by denying parentage to such as exhibit the corresponding character To do so would be to leave the far more numerous heterozygotes untouched In the case of a recessive autosomal

gene, assuming random mating the number of heterozygotes (Aa) in a population is twice the square root of the numbers of the two homozygous classes (AA and aa). Thus if the number of individuals in the (AA) phenotype is $p^2$ and of those in the (aa) phenotype is $q^2$ the three genotypes AA, Aa and aa are distributed in the proportion $p^2$ $2pq$ $q^2$

Thus if a particular autosomal recessive character is exhibited by one in a million of the population the frequency of phenotypically normal individuals heterozygous for this gene is around one in five hundred. The rarer the gene in question the greater the proportion of heterozygotes (Aa) compared to individuals homozygous for this recessive gene. If as many as one in a hundred of the population exhibit a particular recessive character (aa) then the heterozygotes (Aa) will be only eighteen times more numerous than those who exhibit the character

If both prospective parents exhibit the character so also will all their offspring If one of them is affected and the other is unaffected *the latter may be a heterozygote.* A pedigree may provide the evidence. If he or she is a heterozygote then the chances that the child will or will not exhibit the character are equal (Aa × aa = Aa aa) If he or she is not a heterozygote all the offspring will be phenotypically normal but genetically heterozygotes (AA × aa = Aa) If both of the prospective parents are possible heterozygotes the respective pedigrees showing the same defect then the chances that the offspring will be abnormal are one in four (Aa × Aa = 1 AA, 2 Aa, 1 aa)

*An autosomal dominant* (including the partially sex-linked dominant). The pathological characters of this kind that matter are rare and are those that are seriously deleterious and are expressed in the heterozygote. There is no point in denying parentage to the exhibitors. These are remarkable for a diminished viability and reproductivity The (recurrent) mutation rate is usually such as to maintain the low frequency with which the gene is found in the population. Short of devising (chemical?) means for the overwhelming during development of the action of such a gene we must wait until it has become a recessive

If on the other hand, the dominant gene does not equip the exhibitor of the character with lowered viability and

reproductivity and if the mutation rate is low non-propagation on the part of the exhibitors can be expected to diminish the frequency of the gene in the genetical constitution of the population.

But an earnest couple deeply conscious of a responsibility toward their unconceived child will not be interested in these matters. They want to discuss the chances that a particular individual the child they wish to have will be abnormal If one parent exhibits the defect half the offspring can be expected to do so or there is an equal chance that a child will exhibit the character or will not (Aa × aa = Aa aa) It is most unlikely that the affected parent will be homozygous If neither parent is affected though the character is present in their pedigrees they are normals and their offspring will be normal (in the absence of mutation which is very rare)

*A Totally Sex linked Recessive* The male is either normal or else affected he cannot be a carrier The female can be normal a carrier or affected. The only real difficulty *is the identification of the carrier A female is* certainly a carrier if one or other of her parents was affected and the other normal. (AX)Y × (aX)(aX) = *(AX)(aX)* (aX)Y or (aX)Y × (AX)(AX) = *(AX)(aX)* (AX)Y She may be a carrier if her mother was a carrier and her father normal. (AX)Y × (AX)(aX) = (AX)(AX) *(AX)(aX)* (AX)Y (aX)Y She may be a carrier if her mother was a carrier and her father affected (aX)Y × (AX) (aX) = *(AX)(aX)* (aX)(aX) (aX)Y (ax)Y A survey of the close relatives of the parents and of the sibs of the female concerned may furnish considerable aid Reference to the red-green blindness matings will provide the raw material of advice.

## When Penetrance is Low

Low penetrance introduces a serious embarrassment to the offering of firm advice. To say that leukæmia has a penetrance of only about 1 per cent. does not mean in the least that in the child under discussion the character will not be fully expressed There is no telling The prospective parents want to know what the chances are that this particular individual will be affected. They cannot be expected to listen to a learned disquisition and to express admiration for the profundity of one's knowledge.

Consider for example the case of a young man suffering from severe otosclerosis who wishes to marry His father was deaf but the nature of his deafness was not recorded. There is no history of otosclerosis in the prospective bride s family What likelihood is there of a child of this marriage exhibiting this defect ? Otosclerosis can be genetic or non-genetic in origin. When genetic, an autosomal dominant gene with variable penetrance is responsible In his case therefore the question as to the nature of his father s deafness assumes great importance. If nothing can be learnt about this it becomes necessary to assume that it was the genetic form of otosclerosis Then the prospect of a child of the proposed marriage developing the condition would be one in two if penetrance were complete. A careful examination of the medical histories of the sibs of the propositus and of those of his father might show whether penetrance was variable. If it were the prognosis would be improved

## Concerning the Prospects of Sibs Yet to be Conceived

If a phenotypically normal couple have produced a child exhibiting a lethal or seriously irreparable disadvantageous character of undoubted genetic origin towards the ætiology of which environmental agencies have contributed little or nothing they should be advised to have no more. Whenever non-propagation is recommended the question of the adoption of a child of different parentage should be discussed, particular attention being paid to the question of the I Q This is advice derived not from genetical knowledge but from the teachings of the psychologist.

## Consanguinity

The degree of blood relationship now being considered is that which is displayed by individuals whose marriage is permitted by our laws. It is not that degree which is associated with matings regarded by our society and its laws as incestuous. From the purely genetic point of view there is no essential difference between these two in kind but only a difference in degree.

In the case of father × daughter mother × son, brother × sister matings the genetic constitutions of the individuals

concerned include very many genes in common. One half of all the genic material of a daughter has been received from her father one half of all the autosomal material and his X-chromosome have been received by a son from his mother it is highly probable that the genotypes of brother and sister will be far more nearly alike than will those of an unrelated male and female.

If it is accepted that the genotypes of the vast majority if not of all human beings are heavily loaded with undesirable recessive genes which remain impotent so long as the mating of heterozygote × heterozygote does not provide the chance for their expression then incestuous matings must be condemned It must be remembered, moreover that in our society those who indulge in this form of illegal activity are usually such as are unable to accept the current social standards by reason of their mental or moral subnormality innate or acquired Even although their genotypes happened to include no common grossly pathological recessive genes it remains possible that they would be deficient in respect of the genes for high grades of general intelligence. In any case the individuals concerned are commonly quite incapable of providing in the home the kind of environment which is essential for the proper development of the child.

This matter of consanguinity is usually related to the question of the desirability of the marriage of first cousins These share in common a considerable amount of chromosome material received from the same pair of grandparents. It is therefore eminently possible for each of them to be heterozygous in respect of the same recessive gene corresponding to a character of a pathological kind. It is for this reason that inbreeding that breeding system which involves the deliberate mating of near blood relatives has been so useful an instrument in genetical enquiry and in animal and plant improvement. By means of inbreeding the undesirable that is hidden becomes revealed and so a stock can be purged of its unwanted recessives. In the case of man it is highly probable that when the pedigree of an affected child suffering from a very rare recessive character is searched it will be found that its parents are near blood relatives. This is especially so in the case of a female child who exhibits a rare recessive sex-linked character

The frequency of cousin marriages in our society is of the

order of 0 5 per cent Prospective parents who share a common ancestry in which a serious recessive defect has appeared should be informed as to the bearing of consanguinity on the production of homozygotes If in the pedigree there is no record of genetic abnormality it will be difficult to find sufficient cause for advising *non propagation. On general grounds, however* the advice must be that the marriage of near relatives is hazardous and not to be encouraged. In the construction of pedigrees it is to be remembered that there is no great profit in attempting to work back to the P and $P_4$ generations. It is infinitely more important to collect full and accurate records of the parental generation and of the sibs of the couple concerned. A great deal can be made of these.

## Characters Caused by the Interaction of Genetic and Environmental Factors

There is satisfaction in the knowledge that many abnormalities are of this kind since the control of the environmental *factor* renders the genetic factor impotent. *There undoubtedly* is a genetic factor possibly an autosomal dominant with a low penetrance, involved in the ætiology of Mongolism, but the gene(s) that lies at the root of this character requires a special intra-uterine environment if it is to gain expression. The repair of the environment in attempts to eradicate Mongolism would seem to be a far more hopeful task than to endeavour to control the action of the gene or to eliminate it from the population So also in the case of tuberculosis. If the environmental causal factors are mastered the genetic factors can be disregarded. But it has to be noted that by so doing there will remain in the population large numbers of individuals genetically prone and that should the environmental factors ever come into operation through a worsening of the standards of living tuberculosis can become a scourge. The prevention of disease of this kind through the control of the environment demands that this control shall never be relaxed.

## Concerning Mixed Marriages

By mixed is meant the marriage of individuals belonging *to different geographical varieties of homo sapiens* Of these so-called races there are three main stems recognised by

the anthropologist, Whites Yellow Browns and Blacks (Caucasoid mongoloid and negroid) There are subdivisions of each of these. Of the Whites there are hamitic, semitic, Mediterranean Alpine and nordic of the Yellow Browns there are the mongolic, the Malay and the American of the Black there are the negrito the negrillo the bushman and Hottentot and the negro Polynesians and mongoloids would seem to be hybrids between the whites and yellow browns Australians and Papuans hybrids between whites and blacks.

Each geographical variety differs from the others in respect of its genotype and therefore of its phenotype. They are to be distinguished one from the other by reference to such characters as skin colour hair colour texture and distribution, head shape and so forth. They differ in respect of gene content and in the frequency with which certain genes are to be encountered in the population.

All are mutually fertile. Whether or not it is desirable or undesirable *on genetical grounds* for representatives of any two of these varieties to marry *and reproduce* is to be determined by the effect of the pooling of the genotypes. These varieties evolved as isolates. That is to say each, being separated from the rest, evolved its own genotype through mutation and selection Each may have come to possess mutant genes absent from the genotypes of the rest. Each, as the result of mutation and selection, came to be in harmony with its own peculiar external world. It has to be noted, however that in recent times there has been much interbreeding between most if not all of these varieties so that in respect of gene content and frequency all are much more alike than they were when each was an isolate. None of them is pure in the genetical sense any longer for pooling of genotypes has already occurred There is evidence which seems to show that the offspring of certain varietal crosses do exhibit certain anatomical and other disharmonies. On the other hand it is established that many intervarietal hybrids are biologically quite efficient. If man is, in this respect like other animals it would be expected that such offspring would be remarkable for hybrid vigour In every variety there is the same wide range of variation in respect of physical perfection and mental ability although the mean may differ from variety to variety

There certainly is no genetical problem in the intermarriage of representatives of subgroups of any of the main stems, of an Alpine and a Mediterranean, for example There would seem to be none in the intermarriage of white and mongoloid or of white and yellow brown.

The fact is, of course, that usually the different varieties have developed different cultures and are commonly to be distinguished one from the other in respect of ethic, habit and manners Intermarriage is far more than a purely biological adventure it involves the clash of cultures differences in standards, habits values.

The marriage of black and white, for example, usually means that one or other of the partners must become a member of a society in which he or she must remain a stranger Off spring of the marriage, besides being half-castes can be social outcasts for whom there is no place The problems created by the marriage of a Scots girl to a negro are of the same kind as those produced by the marriage of a Roman Catholic and an agnostic or of a Jew and a gentile. They differ only in degree. The desirability or otherwise of such marriages is to be determined by considerations of the social circumstances which will surround the mated pair and their offspring

## Epilogue

Medicine is the means used in the establishment and re-establishment of harmony within the individual and between the individual and his external, physical and social world. It attempts to establish harmony between the individual and his environment by removing from the latter all agencies inimical to the well-being of the inhabitants and to congregate within it all those agencies which promote the development and maintenance of health.

By means of education concerning health and disease, and by vaccination and inoculation or by such measures as paludrine administration, medicine attempts so to modify the characterisation of the individual that he finds himself adjusted to the conditions of the environment and so is enabled to flourish therein

Through the discovery of new knowledge and its incorporation in practice, medicine has gained great powers. The future

will see these greatly augmented. There is no hint as yet however that it will soon become possible so to control mutation and to modify genic action of an undesirable nature that its *effects during development will be checked or reversed. All* that we can hope at present is that in increasing measure surgical, biochemical or other means will be discovered that will repair the abnormality caused by the gene Surgery can repair polydactyly insulin can control diabetes.

The prevention of purely genetic abnormality must take the form of the extirpation where this is possible and desirable through non propagation of the genes concerned from the genetic constitution of the population. It must remain *impossible to advocate non propagation until our knowledge* of the aetiology of many of these conditions is far more exact and conclusive.

We have learnt that environments differ in respect of their ingredients. We have learnt also that in a human population there are many different phenotypes based on different genotypes No environment is optimal for all genotypes, no single genotype can provide phenotypes attuned to all environments Diversity in characterisation is desirable in a human society *In the ideal society there should be both environmental and* genotypic variety Medicine should aim at the elimination of all environments which prevent or hinder the expression of those genetic qualities which are biologically and socially valuable and at the eradication from the population of those genotypes which render their possessors incapable of flourishing in any of the varieties of environment that are propitious for the manifestation of biologically worthy genetic endowments.

There may come a time when in our programmes for the achievement of human perfection we may wish to treat genetic disease by genetical therapeusis. For this reason it is desirable that even now every effort should be made to expand our knowledge of human genetics in order that if required the appropriate instruments of therapy may be found sharpened and ready in the medical armamentarium. One purpose of this book has been to enlist the co-operation of its readers in th

The student is advised to make use of the followin for further reading

BLACKER, C. P (1934). *The Chances of Morbid Inheritance* Lewis,

COCKAYNE, E. A. (1933). *Inherited Abnormalities of the Skin Appendages* Oxford University Press, London.

CREW F A. E. (1933). *Sex Determination* Methuen, London.

DARLINGTON C. D (1937). *Recent Advances in Cytology* Ch London.

FISHER, R. A. (1930). *The Genetical Theory of Natural Selection.* C University Press, London.

FORD E. B. (1940). *Mendelism and Evolution.* Methuen, London.

FORD, E. B (1946). *Genetics for Medical Students* Methuen, London.

GATES, R. R. (1946). *Human Genetics* Macmillan, New York.

GOLDSCHMIDT R. (1938). *Physiological Genetics* McGraw Hill, N York and London.

GRUNEBERG, H. (1947). *Animal Genetics and Medicine* Ham Hamilton, London.

HALDANE, J B. S. (1932) *The Causes of Evolution* Longmans London.

HALDANE, J B S (1938) *Heredity and Politics* Allen and Unwin London.

HALDANE, J B. S (1941). *New Paths in Genetics* Allen and Unwin,

HALDANE, J B S (1946). The Formal Genetics of Man. Croonian Lecture, Royal Society of London. *Proc Roy Soc* (British).

HILL, BRADFORD (1942). Principles of Medical Statistics, *Lancet* London.

HOGBEN L. T (1939). *Nature and Nurture* Allen and Unwin, London.

HOGBEN L. T (1947). *An Introduction to Mathematical Genetics* W W Norton, New York.

MATHER, K. (1938) *The Measurement of Linkage in Heredity* Methuen, London.

PENROSE, L. S. (1934) *The Influence of Heredity on Disease* Lewis, London.

PUFFER, R. R. (1946). *Familial Susceptibility to Tuberculosis* Harvard University Press.

ROBERTS, J A. FRASER (1940) *An Introduction to Medical Genetic* Oxford University Press, London.

SCHEINFELD A. (1939) *You and Heredity* Chatto and Windus, London.

WADDINGTON C H. (1939). *An Introduction to Modern Genetics* Allen and Unwin London.

WHITE, M J D (1937). *The Chromosomes* Methuen, London.

Attention should also be paid to the following journals —

*The Journal of Genetics* (British)
*Genetics* (American).
*The Journal of Heredity* (American).
*Heredity* (British).
*The Annals of Eugenics* (British).
*Eugenics Review* (British).
*Biometrica* (Brit